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# Total Synthesis of (-)-Calyciphylline N

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**Abstract**
The dissertation herein describes the first total synthesis of the complex Daphniphyllum alkaloid, (-)-calyciphylline N. This alkaloid was chosen as the target in our synthetic program due its unprecedented structure, the inherent challenges associated with its synthesis, and limited reports of synthetic studies towards members of this family of natural products. An initial unsuccessful approach is discussed, followed by a revised, ultimately successful approach. Highlights of the synthesis include a substrate controlled, intramolecular Diels-Alder reaction to build the bicyclo[2.2.2]octane core and set four contiguous stereocenters, a transannular enolate alkylation to secure ring D, a highly efficient Stille carbonylation/ Nazarov cyclization sequence to construct ring E with concomitant activation of a hindered silyl group towards Fleming-Tamao oxidation, and an unprecedented, homogeneous hydrogenation of an exceptionally hindered diene ester to complete the eastern hemisphere, a structural motif that is common to a variety of the Daphniphyllum alkaloids.

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# TOTAL SYNTHESIS OF (–)-CALYCIPHYLLINE N

Artem Shvartsbart

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# ABSTRACT


## TOTAL SYNTHESIS OF (–)-CALYCIPHYLLINE N

Artem Shvartsbart

Amos B. Smith, III

The dissertation herein describes the first total synthesis of the complex *Daphniphyllum* alkaloid, (–)-calyciphylline N. This alkaloid was chosen as the target in our synthetic program due its unprecedented structure, the inherent challenges associated with its synthesis, and limited reports of synthetic studies towards members of this family of natural products. An initial unsuccessful approach is discussed, followed by a revised, ultimately successful approach. Highlights of the synthesis include a substrate controlled, intramolecular Diels-Alder reaction to build the bicyclo[2.2.2]octane core and set four contiguous stereocenters, a transannular enolate alkylation to secure ring D, a highly efficient Stille carbonylation/Nazarov cyclization sequence to construct ring E with concomitant activation of a hindered silyl group towards Fleming-Tamao oxidation, and an unprecedented, homogeneous hydrogenation of an exceptionally hindered diene ester to complete the eastern hemisphere, a structural motif that is common to a variety of the *Daphniphyllum* alkaloids.

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## List of Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| $Ac_2O$ | Acetic anhydride |
| aq. | Aqueous |
| $BF_3•OEt_2$ | Boron trifluoride diethyl etherate |
| Bn | Benzyl |
| BuLi | *n*-Butyllithium |
| *t*-BuLi | *tert*-Butyllithium |
| Bz | Benzoyl |
| $Bz_2O$ | Benzoic anhydride |
| DCE | 1,2-Dichloroethane |
| DEAD | Diethyl azodicarboxylate |
| DIBAL-H | Diisobutylaluminum hydride |
| DMP | Dess-Martin periodinane |
| DMAP | 4-Dimethylaminopyridine |
| DMF | *N,N*-Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| d.r. | Diastereomeric ratio |

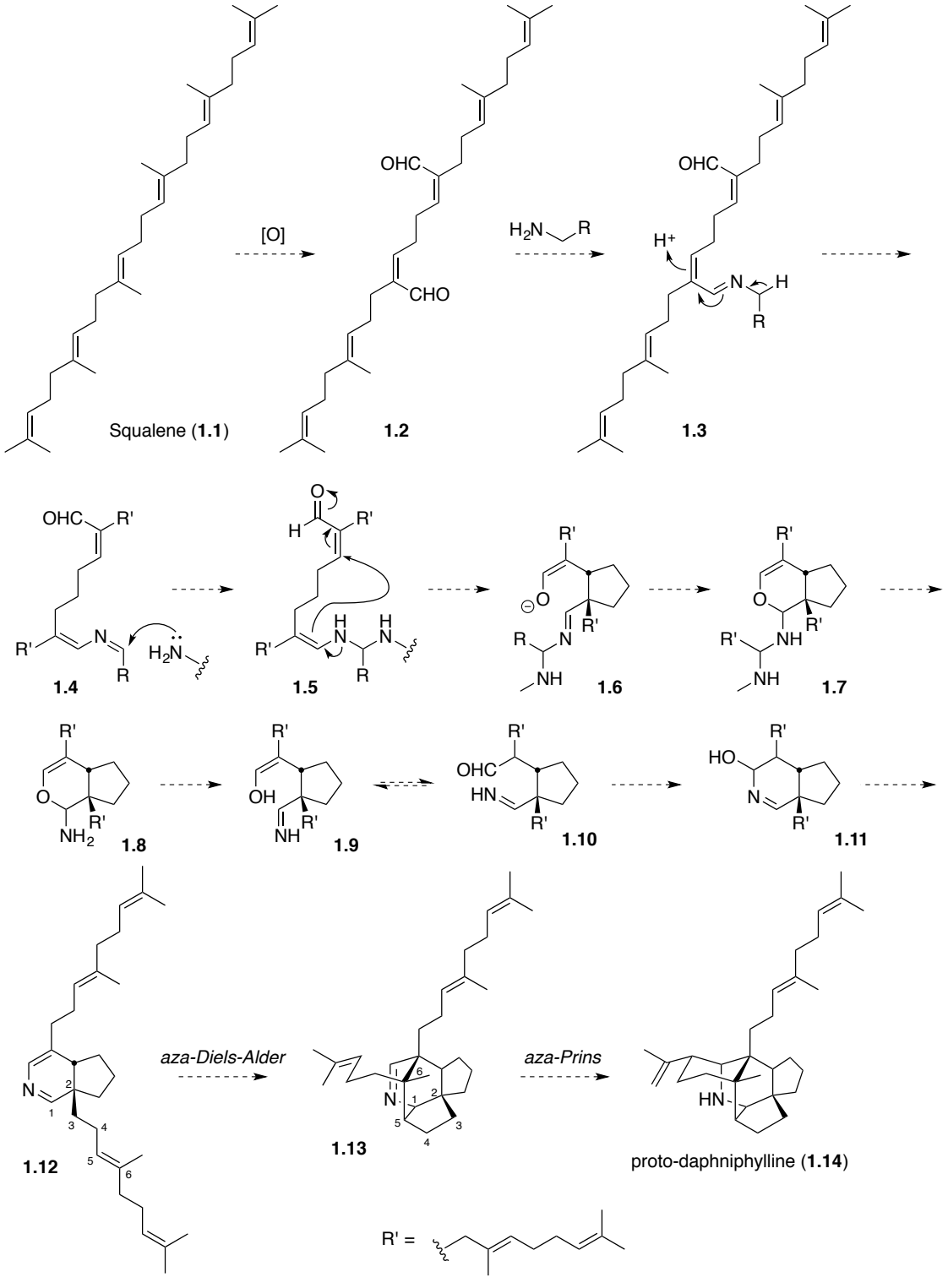
| | |
|---|---|
| ESI | Electrospray ionization |
| $Et_2O$ | Diethyl ether |
| $Et_3N$ | Triethylamine |
| EtOAc | Ethyl acetate |
| HCl | Hydrochloric acid |
| HMBC | Heteronuclear multiple-bond correlation |
| HSQC | Heteronuclear single quantum correlation |
| HRMS | High resolution mass spectrum |
| *i*-PrMgCl | Isopropylmagnesium chloride |
| *i*-$Pr_2NEt$ | Diisopropylethylamine |
| KHMDS | Potassium hexamethyldisilazide |
| LCMS | Liquid chromatography mass spectrometry |
| LDA | Lithium diisopropylamide |
| *m*-CPBA | *meta*-Chloroperoxybenzoic acid |
| Me | Methyl |
| MHz | Megahertz |
| MOM | Methoxymethyl |
| MPLC | Medium pressure liquid chromatography |
| NaHMDS | Sodium hexamethyldisilazide |
| NMR | Nuclear magnetic resonance |
| NOESY | Nuclear Overhauser effect spectroscopy |
| Nu | Nucleophile |

| | |
|---|---|
| $Pd(PPh_3)_4$ | Palladium tetrakis(triphenylphosphine) |
| Ph | Phenyl |
| Piv | Pivaloyl |
| PPTS | Pyridinium *para*-toluenesulfonate |
| TBAF | Tetrabutylammonium fluoride |
| TBS | *tert*-Butyldimethylsilyl |
| TBSCl | *tert*-Butyldimethylsilyl chloride |
| TEMPO | 2,2,6,6-Tetramethylpiperidine-1-oxyl |
| TES | Triethylsilyl |
| TfOH | Trifluoromethanesulfonic acid |
| THF | Tetrahydrofuran |
| TLC | Thin-layer chromatography |
| TOCSY | Total correlation spectroscopy |

# CHAPTER 1:
# The Daphniphyllum Alkaloids

## 1-1: Isolation and Biosynthesis

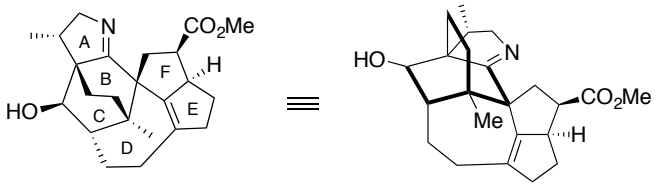
Plants of the *Daphniphyllum* genus, found in central and southern Japan, China, Taiwan, and New Guinea, produce a series of complex alkaloids with over 200 known members.[1] These natural products have been classified based on six members; daphnipylline, secodaphniphylline, yuzurimine, daphnilactone A, daphnilactone B, and yuzurine.[2] There are also a variety of new additions with unprecedented structures. Given the diversity in structure, the *Daphniphyllum* alkaloids have attracted great interest for biosynthetic studies and as challenging targets for total synthesis.[3] In the late 1980s, Heathcock and co-workers proposed a biosynthetic pathway,[4] which culminated in several elegant biomimetic total syntheses.[5] This pathway begins with the oxidation of squalene (**1.1**) to the squalene dialdehyde species **1.2** (Scheme 1.1). Condensation of a primary amine (such as an amino acid) with one of the aldehyde groups would give rise to the 1-azadiene **1.3**, which can undergo a prototropic shift to the corresponding 2-azadiene **1.4**. Heathcock proposed that a nitrogen nucleophile adds to C(1) of the azadiene to produce the nucleophilic enamine **1.5**. Intramolecular Michael addition, followed by cyclization of the resulting enolate affords **1.7**. A series of proton mediated addition and elimination processes would ultimately transform **1.7** to the 2-aza-cyclohexadiene **1.12**. An intramolecular aza-Diels-Alder reaction, followed by an aza-Prins cyclization results in the formation of proto-daphniphylline (**1.14**), which is believed to be a common intermediate in the biosynthesis of all the *Daphniphyllum* alkaloids.




**Scheme 1.1:** Biosynthesis of Proto-Daphniphylline

## 1-2: (–)-Calyciphylline N

In 2008, Kobayashi and co-workers reported the isolation of (–)-calyciphylline N (**1.15**, Figure 1) from *Daphniphyllum calycinum*; the structural determination was based on extensive NMR analysis, as well as comparison to congeners within the family.[6] The biological activity of **1.15**, however, has yet to be explored. Calyciphylline N possesses a unique and intricately complex molecular architecture, consisting of a cagelike, hexacyclic ring system. Notable structural features include the dihydropyrrole A ring of the western hemisphere and the decahydrocyclopentazulene DEF ring system of the eastern hemisphere, surrounding a central bicyclo[2.2.2]octane BC core. Additionally, the molecule possesses six contiguous stereocenters with a total of eight stereocenters, three of which are bridgehead, quaternary centers. To date, neither (–)-calyciphylline N, nor any member of the calyciphylline family of alkaloids has succumbed to total synthesis. This fact, as well as the inherent challenge associated with a synthetic effort towards this intriguing natural product, rendered this work a worthwhile endeavor.

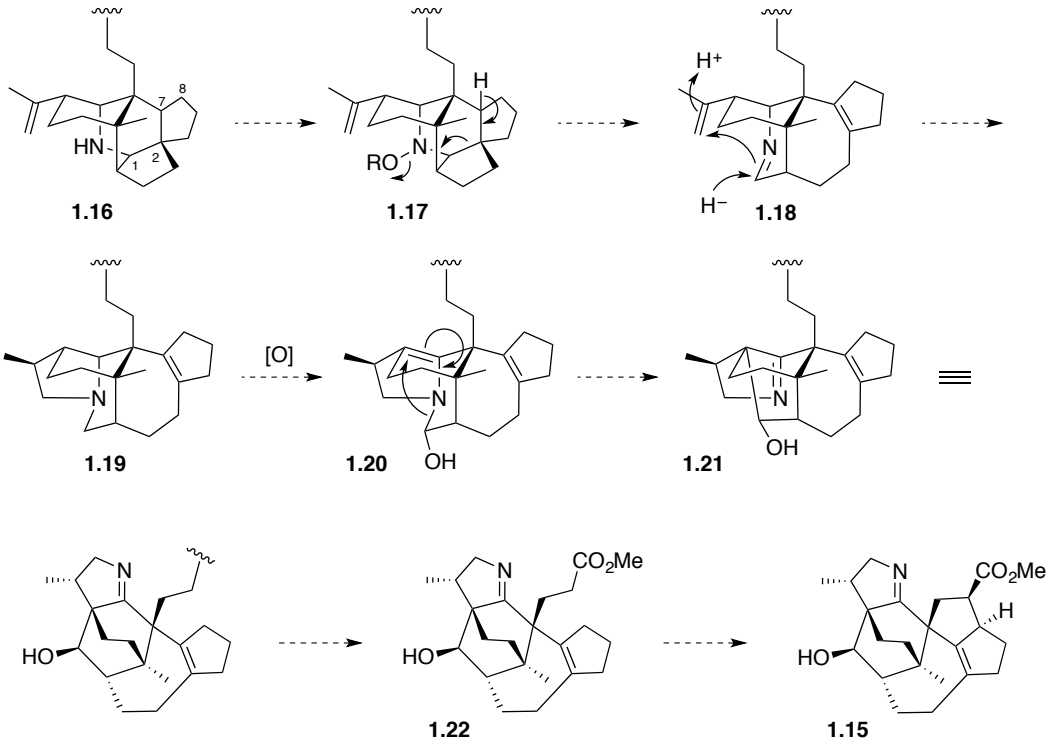



(–)-Calyciphylline N (**1.15**)

**Figure 1.1:** Structure of (–)-Calyciphylline N

Biosynthetically, **1.15** can be envisioned to arise from a proto-daphniphylline type intermediate **1.16** by the sequence shown in Scheme 1.2.[7] Oxidation of the amine in **1.16** would give **1.17**, which could undergo a Grob-type fragmentation by loss of the proton at C(7) and cleavage of the C(1)-C(2) bond. Reduction of the resulting imine with concomitant cyclization onto the isopropenyl side chain would then give **1.19**. A series of

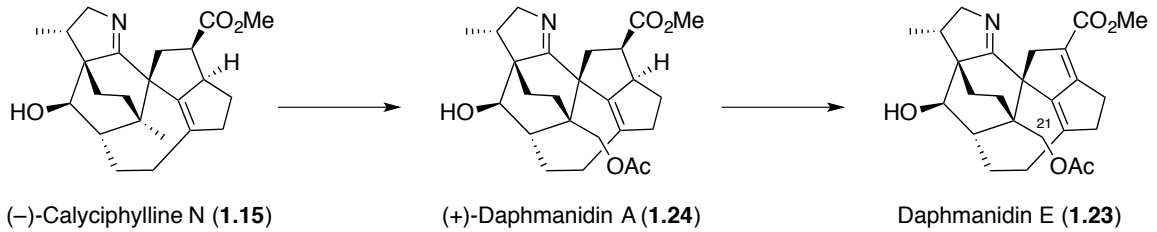
oxidations leads to **1.20**, which rearranges to **1.21**. Functionalization of the side chain, followed by formation of a bond between the α carbon of the ester and C(8) would provide **1.15**.




**Scheme 1.2:** Proposed Biosynthesis of Calyciphylline N

## 1-3: The Carreira Synthesis of (+)-Daphmanidin E

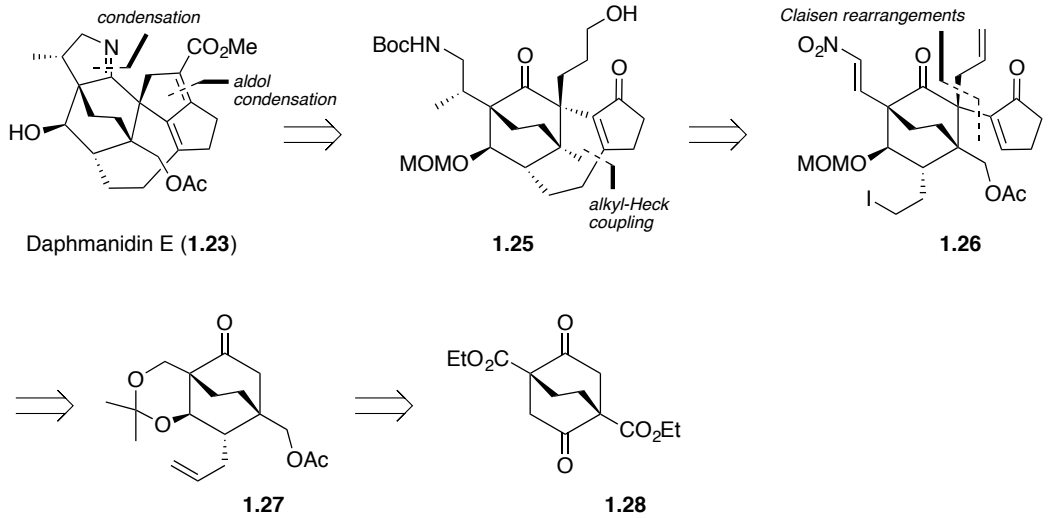
In 2011, during the course of our work, Carreira and Weiss reported the total synthesis of the closely related congener, (+)-daphmanidin E (**1.23**, Scheme 1.3).[3e] Daphmanidin E differs from (–)-calyciphylline N by the presence of an acetoxy group at C(21) [(–)-calyciphylline N numbering], as well as a conjugated olefin within the F ring. Calyciphylline N is a putative biosynthetic precursor of (+)-daphmanidin E,[8] through the intermediacy of (–)-daphmanidin A (**1.24**).




(–)-Calyciphylline N (**1.15**) (+)-Daphmanidin A (**1.24**) Daphmanidin E (**1.23**)

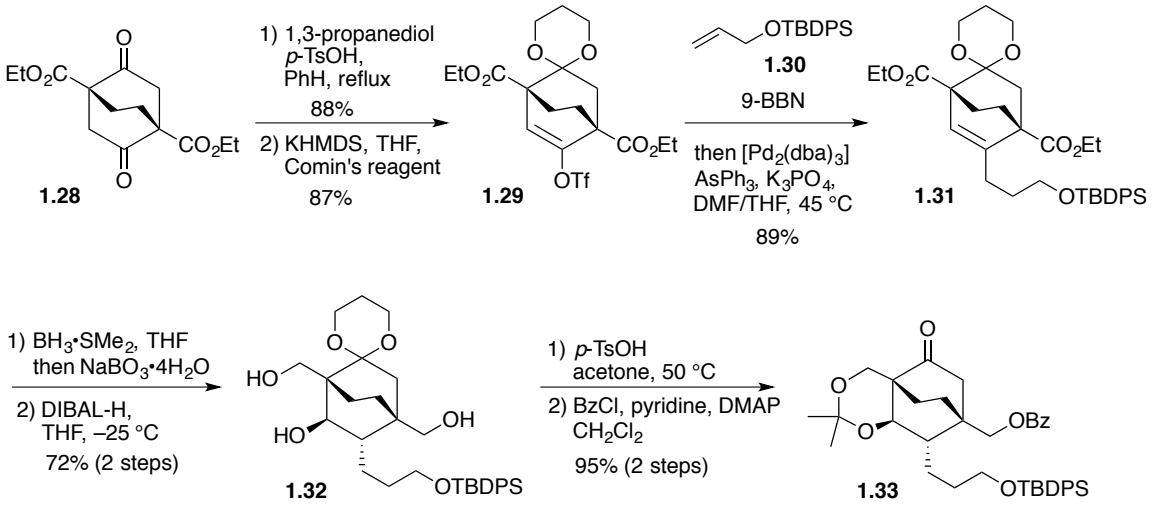
**Scheme 1.3:** Biosynthetic Relationship Between (–)-Calyciphylline N and (+)-Daphmanidin E

Carreira's retrosynthetic analysis of (+)-daphmanidin E is outlined below (Scheme 1.4). The A ring was envisioned to arise via condensation of a primary amine with the B ring ketone, while the bis-unsaturated ester could be constructed by an aldol condensation, simplifying the target to tetracycle **1.25**. An alkyl-Heck coupling was envisaged to access the D ring, with the C(20) methyl group installed by a reagent controlled conjugate addition to a nitroalkene. Carreira anticipated that the C(8) quaternary center could be constructed by a series of Claisen rearrangements, further simplifying the structure to acetonide **1.27**, which could then be accessed through elaboration of the optically pure, $C_2$ symmetric diester **1.28**.




**Scheme 1.4:** Carreira retrosynthetic analysis of (+)-daphmanidin E

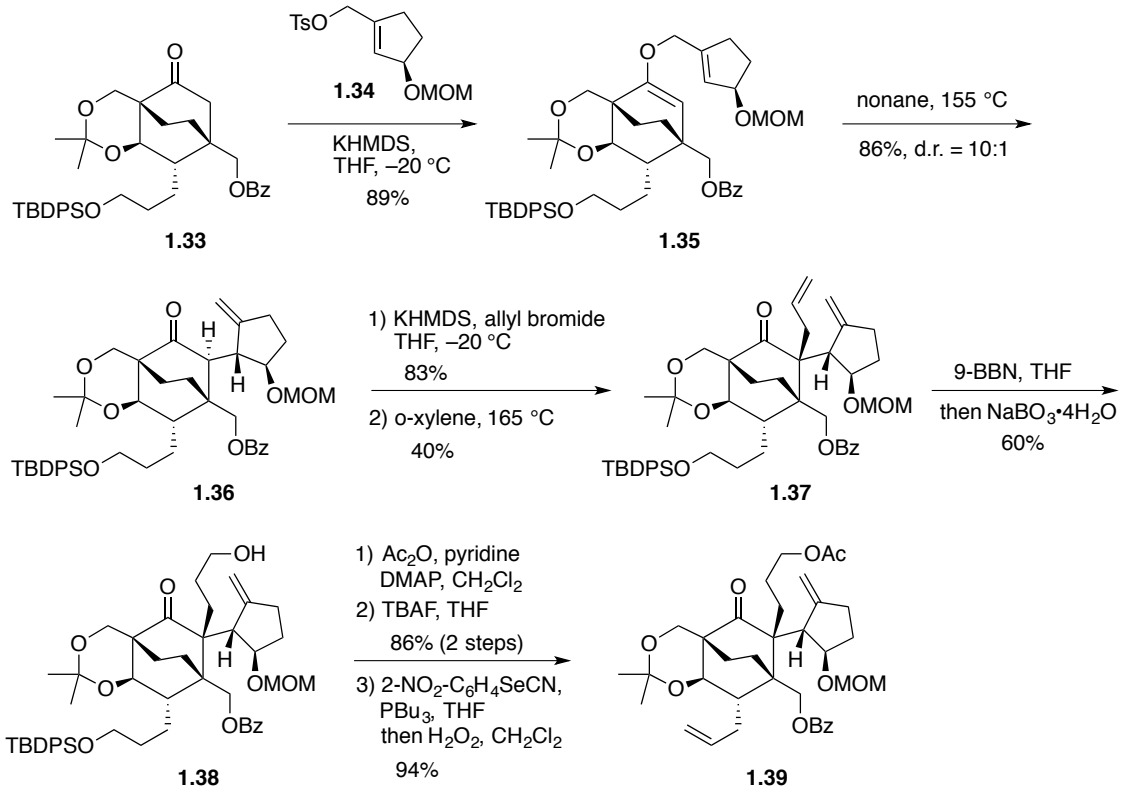
The Carreira synthesis of (+)-daphmanidin E begins with mono-ketalization of **1.28** (1,3-propanediol), followed by conversion of the remaining ketone to the corresponding vinyl triflate to provide **1.29** (Scheme 1.5). Triflate **1.29** underwent a *B*-alkyl Suzuki coupling with the borane derived from TBDPS protected allyl alcohol (**1.30**) to furnish olefin **1.31** in 89% yield. Diastereoselective hydroboration, followed by exhaustive reduction of the ester functionalities then delivered triol **1.32**, the structure of which was confirmed by X-ray crystallography. The 1,3-diol was then selectively protected as the acetonide, and the remaining primary alcohol was protected as a benzoate ester, providing **1.33** in 95% yield over 2 steps.




**Scheme 1.5:** Synthesis of Ketone **1.33**

The next goal was the construction of the C(8) quaternary center. Alkylation of **1.33** with tosylate **1.34** provided allyl vinyl ether **1.35**, which underwent thermal rearrangement upon heating at 155 °C in nonane to afford **1.36** in 86% yield with 10:1 diastereomeric ratio (d.r.). Allylation of ketone **1.36** and subsequent Claisen rearrangement then provided **1.37** in 40% yield, completing the installation of the quaternary

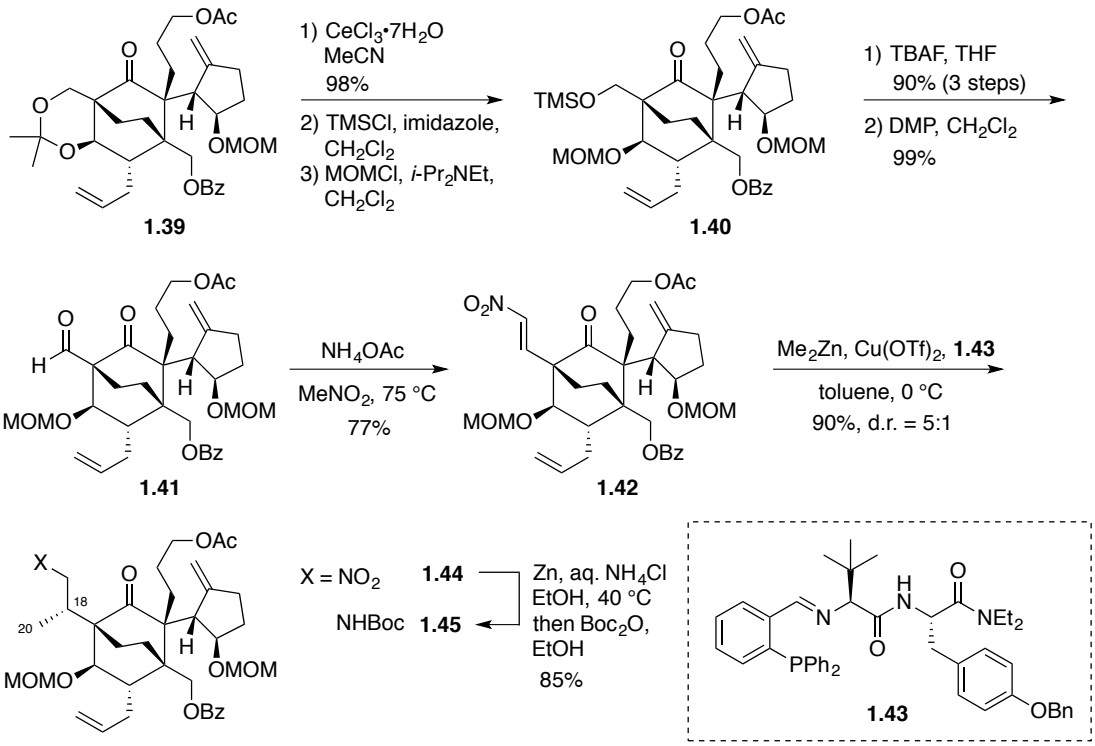
center (Scheme 1.7). Selective hydroboration of the monosubstituted olefin delivered alcohol **1.38** in 60% yield. After protection of the resulting primary alcohol with $Ac_2O$, the TBDPS group was removed with TBAF, and the resulting alcohol was subjected to Grieco dehydration to provide ketone **1.39** in good yield over the 3 steps.




**Scheme 1.6:** Synthesis of Ketone **1.39**

Next, Carreira and Weiss opted to explore installation of the C(18) stereocenter, as well as introduce a suitable precursor for the amine found in the natural product (Scheme 1.7). To this end, hydrolysis of the acetonide, followed by differentiation of the primary and secondary alcohols provided orthogonally protected diol **1.40**. Removal of the TMS group and DMP oxidation of the resulting alcohol delivered aldehyde **1.41**, which was condensed with $MeNO_2$ to furnish nitroalkene **1.42** in 77% yield. Carreira and Weiss

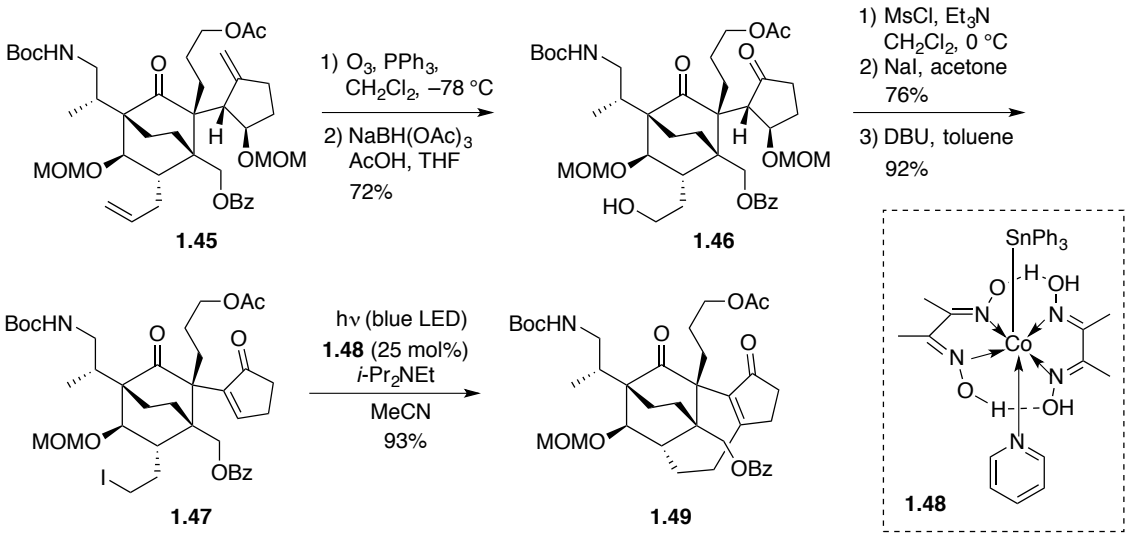
discovered that treatment of **1.42** with $Me_2Zn$ in the presence of $Cu(OTf)_2$ and chiral ligand **1.43** resulted in a reagent controlled conjugate addition to install the C(20) methyl group in 90% yield with 5:1 d.r. Reduction of the nitro group in **1.44** with Zn and $NH_4Cl$, followed by treatment with $Boc_2O$ delivered the Boc protected primary amine **1.45**.




**Scheme 1.7:** Synthesis of Amine **1.45**

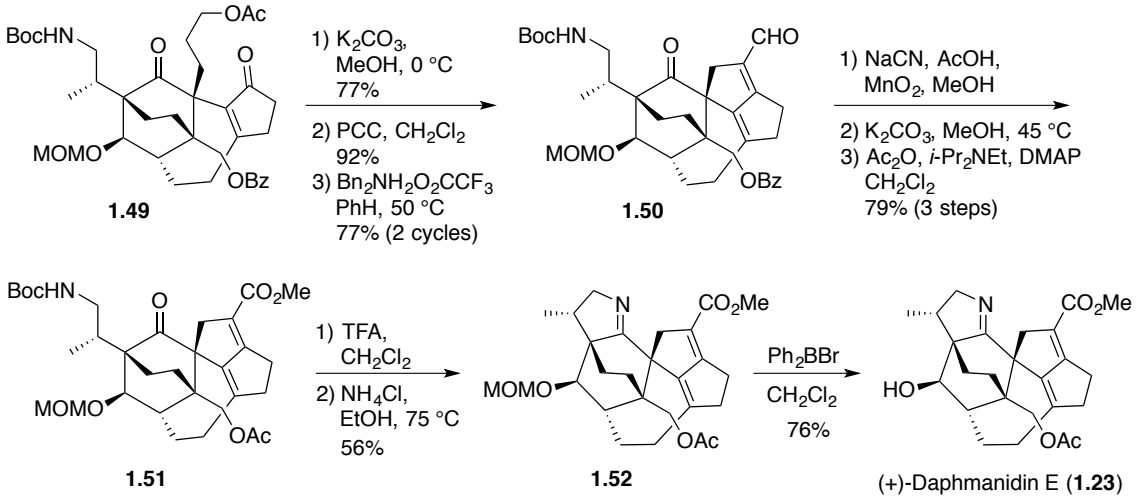
Ozonolysis of **1.45**, followed by selective reduction of the aldehyde then afforded alcohol **1.46** in 72% yield (Scheme 1.8). Conversion of the primary alcohol to the corresponding iodide was next achieved by activation of the hydroxyl group with MsCl with subsequent displacement with NaI. Finally, treatment with DBU resulted in elimination of the MOM group to furnish cyclopentenone **1.47**. Finally, treatment of **1.47** with catalytic cobaloxime **1.48** and stoichiometric *i*-$Pr_2NEt$ under irradiation with blue

light emitting diode (LED) led to the cyclized product **1.49** in 93% yield.




**Scheme 1.8:** Synthesis of Enone **1.49**

Removal of the acetate protecting group and oxidation of the primary alcohol then afforded the corresponding aldehyde, which underwent an aldol condensation upon heating with $Bn_2NH_2O_2CCF_3$ to provide α, β, γ, δ-unsaturated aldehyde **1.50** (Scheme 1.9). Oxidation of the aldehyde and exchange of the benzoate for an acetate group delivered methyl ester **1.51**. Removal of the *N*-Boc group was next achieved with catalytic TFA, and the resulting primary amine was condensed to the imine by heating the ammonium salt in EtOH at 75 °C. Finally, removal of the MOM acetal with $Ph_2BBr$ delivered (+)-daphmanidin E in 76% yield.




**Scheme 1.9:** Completion of the Total Synthesis of (+)-Daphmanidin E

In summary, the total synthesis of (+)-daphmanidin E was completed with a longest linear sequence of 38 steps from commercially available materials, with a total count of 41 steps. It is surprising that Carreira did not continue this work to the monounsaturated system, as one additional step would complete the synthesis of (–)-daphmanidin A (**1.24**).

## 1-4: References


1. Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936-962.

2. (a) Kobayashi, J.; Morita, H., in *"The Alkaloids"* (Cordell, G. A., ed.), Academic Press: New York, 2003, vol. 60, pp. 165-205. (b) Yamamura, S., in *"The Alkaloids"* (Brossi, A., ed.), Academic Press: New York, 1986, vol. 29, pp. 265-286. (c) Yamamura, S.; Hirata, Y., in *"The Alkaloids"* (Manske, R. H. F., ed.), Academic Press: New York, 1975, vol. 15, pp. 41-81.

3. (a) Coldham, I.; Watson, L.; Adams, H.; Martin, N. G. *J. Org. Chem.* **2011**, *76*, 2360-2366. (b) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 1684-1687. (c) Lu, Z. Y.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679-684. (d) Sole, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461-5464. (e) Weiss, M. E.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11501-11505.

4. Ruggeri, R. B.; Heathcock, C. H. *Pure Appl. Chem.* **1989**, *61*, 289-292.

5. (a) Heathcock, C. H. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 14323-14327. (b) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544-2553. (c) Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120-1130. (d) Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3714-3715. (e) Stafford, J. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5433-5434.

6. Yahata, H.; Kubota, T.; Kobayashi, J. *J. Nat. Prod.* **2008**, *72*, 148-151.

7. Kobayashi, J.; Ueno, S.; Morita, H. *J. Org. Chem.* **2002**, *67*, 6546-6549.

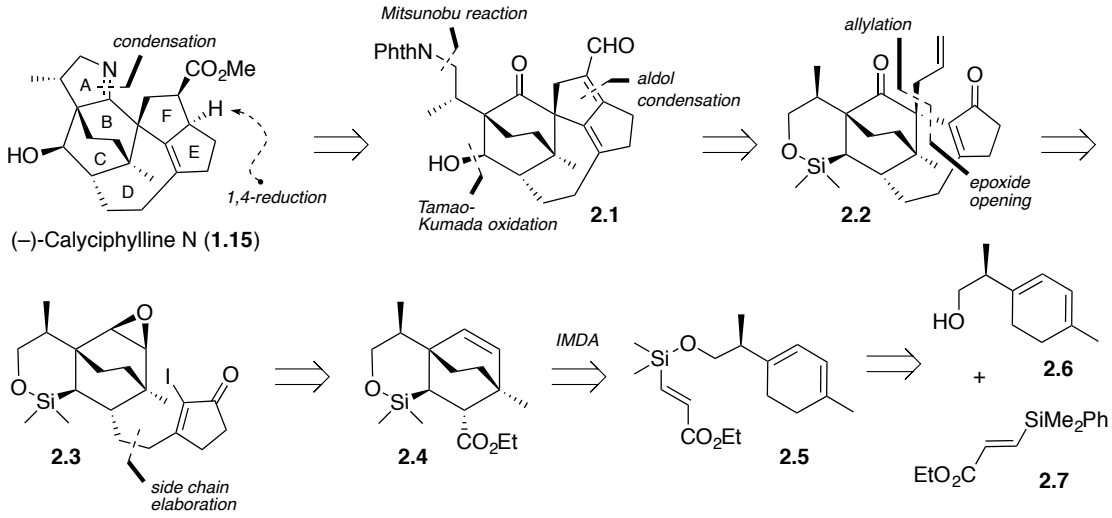
8. Morita, H.; Ishioka, N.; Takatsu, H.; Iizuka, T.; Kobayashi, J. *J. Nat. Prod.* **2006**, *69*, 418-420.

# CHAPTER 2:

# An Initial Synthetic Strategy Towards (–)-Calyciphylline N

## 2-1: Retrosynthetic Analysis

From the retrosynthetic perspective (Scheme 2.1), the dihydropyrrole (A) ring in **1.15** could be constructed by a late stage condensation of a primary amine with the B ring carbonyl. We anticipated that the stereochemistry of the EF ring system could in turn be set by a chemo- and diastereoselective 1,4-reduction of a bis-unsaturated aldehyde or ester, simplifying the target compound to intermediate **2.1**. Installation of the nitrogen could then be accomplished by a Mitsunobu reaction,[1] whereas the C ring secondary hydroxyl would be revealed via a Tamao-Kumada oxidation.[2] Notably, this strategy permits the reactive functionality of the western hemisphere to be masked as a relatively unreactive cyclic siloxane. An aldol condensation should permit the formation of the bis-unsaturated aldehyde, further simplifying the structure to diketone **2.2**. The key step of the synthesis relies upon an intramolecular epoxide ring opening by a carbanion derived from iodo-cyclopentenone **2.3**. Side chain elaboration then traces back to the bicyclic ester **2.4**, which was envisaged to arise from an intramolecular Diels-Alder (IMDA) reaction.[3] Finally, the requisite triene **2.5** could be realized through the union of homoallyic alcohol **2.6** and known silylacrylate **2.7**.[4]

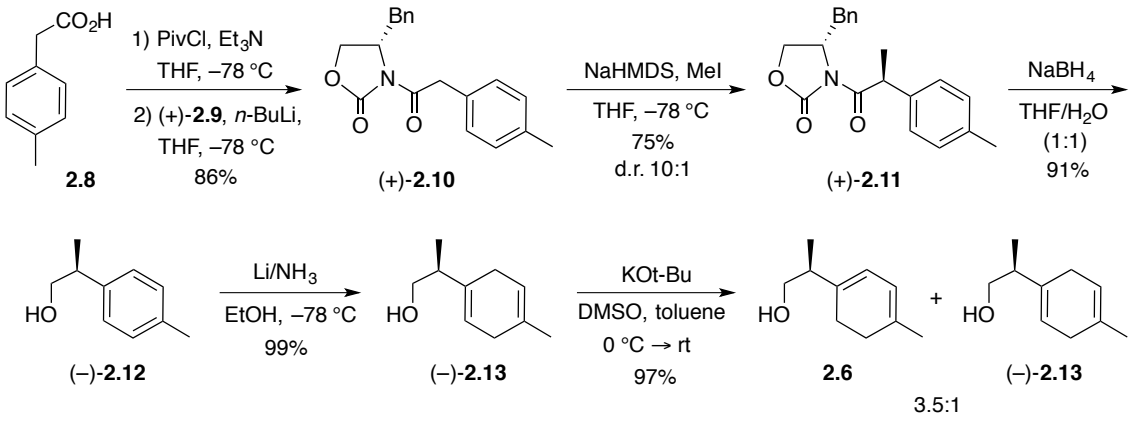



**Scheme 2.1:** Retrosynthetic Analysis

## 2-2: Synthesis of Diene 2.6

The synthesis of diene **2.6** began with commercially available *p*-tolylacetic acid (**2.8,** Scheme 2.2). Conversion of **2.8** to the mixed anhydride was achieved by treatment with pivaloyl chloride and $Et_3N$ at –78 °C. Addition of lithiated (*S*)-4-benzyl-2-oxazolidinone [(+)-**2.9**] *in situ* at –78 °C furnished imide (+)-**2.10** in 86% yield.[5] Enolization of (+)-**2.10** with NaHMDS and alkylation with MeI then delivered the methylated derivative (+)-**2.11** in 75% yield with 10:1 d.r.[6] The diastereomers from the methylation were readily separable by flash chromatography; removal of the chiral auxiliary was then accomplished under mild conditions employing 4 equivalents of $NaBH_4$ in a mixture of THF/$H_2O$ (1:1) at room temperature.[7] Distillation of the residue provided the enantiomerically pure alcohol (–)-**2.12** in 91% yield. Birch reduction[8] of (–)-**2.12** cleanly afforded the expected 1,4-cyclohexadiene (–)-**2.13** as the only product. Exposure of (–)-**2.13** to potassium *tert*-butoxide in DMSO/toluene[9] resulted in olefin isomerization to give an inseparable mixture of **2.6** to (–)-**2.13** (3.5:1, respectively). Attempts to increase this

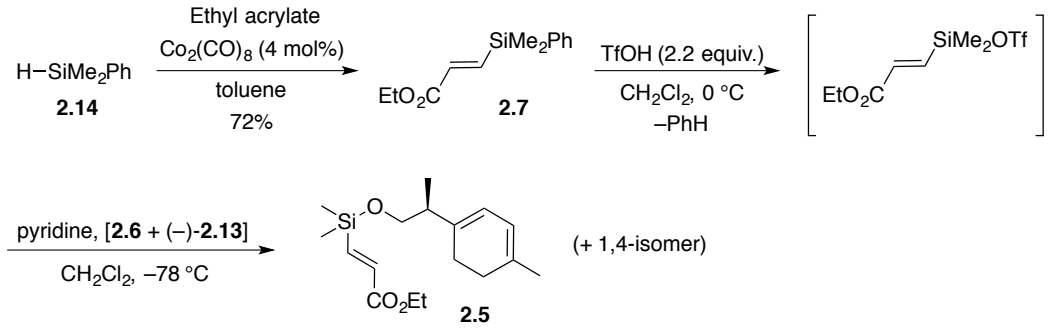
ratio via longer reaction times and higher temperatures proved unsuccessful. Furthermore, we also noted that these dienes were somewhat unstable, undergoing aromatization and other decomposition pathways upon prolonged storage. Therefore, these dienes were prepared and used as quickly as possible.




**Scheme 2.2:** Synthesis of Diene **2.6**

## 2-3: Synthesis of the Bicyclo[2.2.2]octane core

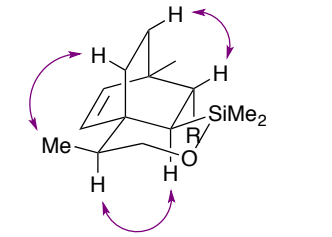
Silylacrylate **2.7** was prepared in 72% yield by a cobalt catalyzed, oxidative hydrosilylation of ethyl acrylate with phenyl dimethylsilane (**2.14**, Scheme 2.3).[4] Utilizing a method introduced by Sieburth,[10] treatment of **2.7** with 2.2 equivalents of TfOH in $CH_2Cl_2$ at 0 °C resulted in rapid protodesilylation to afford the corresponding silyl triflate with liberation of benzene. Addition of pyridine *in situ* at –78 °C, followed by a solution of the alcohols **2.6** and (–)-**2.13** in $CH_2Cl_2$ furnished the requisite triene **2.5**. This compound proved unstable to silica gel chromatography and was therefore carried forward without purification.




**Scheme 2.3:** Synthesis of Triene **2.5**

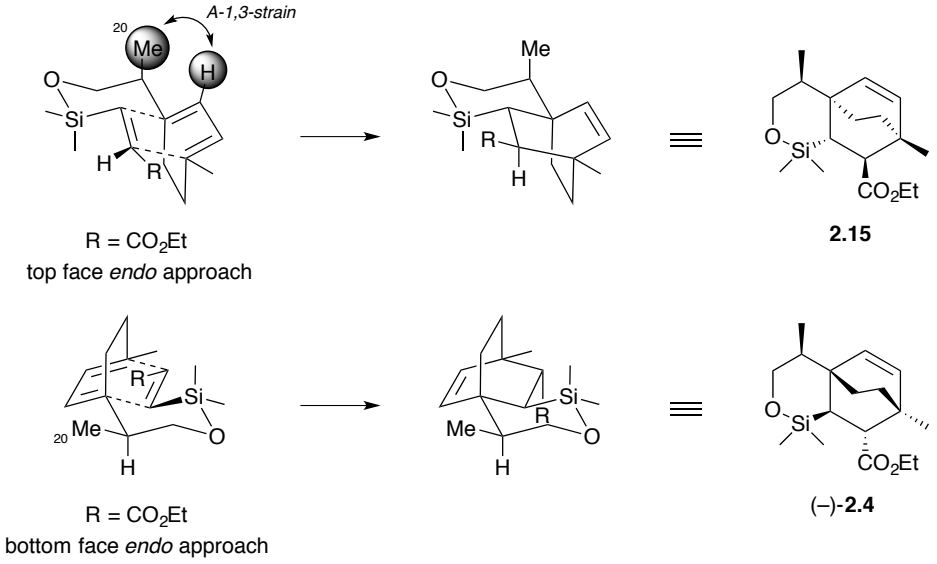
A number of conditions were investigated to induce the proposed IMDA reaction (Scheme 2.4). Thermal cyclization produced a complex mixture of all possible diastereomers (as determined by $^1$H NMR), while the weak Lewis acid $ZnCl_2$ was ineffective. On the other hand, the very strong Lewis acid, $TiCl_4$, resulted in decomposition of the substrate. Pleasingly, $Et_2AlCl$ promoted the cycloaddition to afford a mixture of only two diastereomers in 50% yield from **2.6** with 9:1 selectivity. Careful analysis of the NOESY spectrum confirmed that the desired diastereomer (–)-**2.4** was the major product.


| Entry | Conditions | Result |
|---|---|---|
| 1 | toluene, reflux | Mixture of 4 diastereomers |
| 2 | $TiCl_4$, toluene, –78 °C → rt | Decomposed |
| 3 | $ZnCl_2$, toluene, rt | No reaction |
| 4 | $Et_2AlCl$, toluene, 0 °C | 9:1 mixture of diastereomers; 50% from **2.6** |




**Scheme 2.4:** Diels-Alder Cyclization of Triene 2.5; NOESY Correlations of the Major Diastereomer

The high stereoselectivity observed in this reaction may be rationalized by the following transition state models. Given the known preference for dienophiles to approach the diene π system in an *endo* fashion,[11] the two possible *endo* transition states are presented below (Scheme 2.5). The first transition state depicts an *endo* approach of the dienophile from the top face of the cyclohexadiene, while the second transition state depicts an *endo* approach from the bottom face. By coordinating to the Lewis basic oxygen of the ester, $Et_2AlCl$ lowers the LUMO of the dienophile, which in turn lowers the activation barrier for the cyclization. With the reaction occurring at a much lower temperature (25 °C vs. 110 °C), the transition states that are higher in energy and that would lead to the undesired diastereomers, cannot be attained.




**Scheme 2.5:** Diels-Alder Transition State Analysis

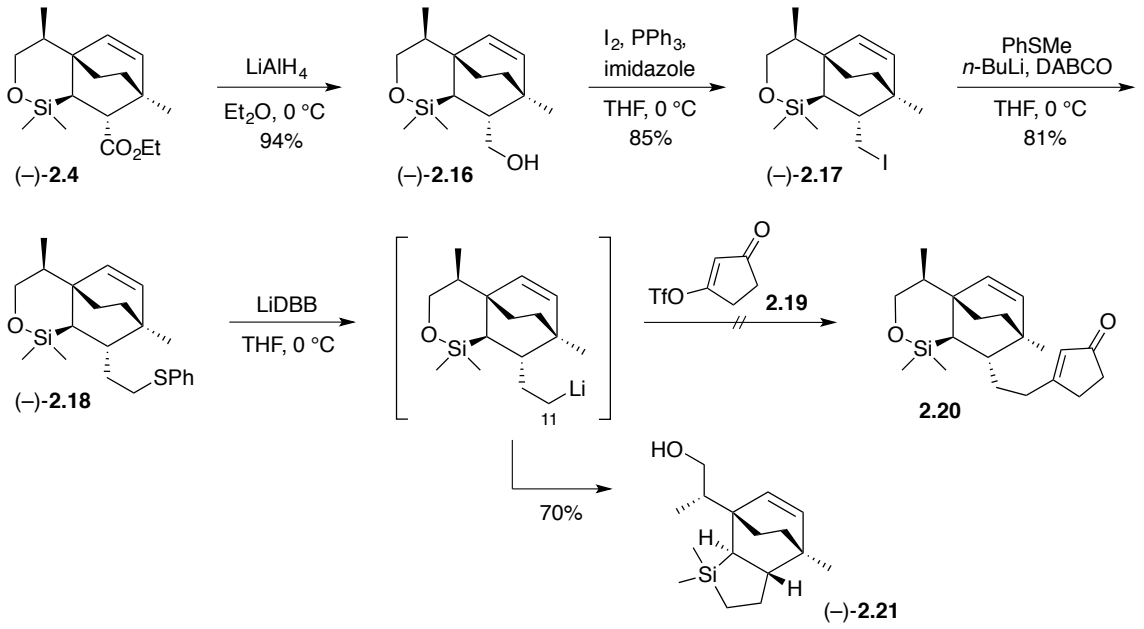
Assuming that the tether adopts a chair conformation in the transition state, an *endo* approach of the dienophile from the top face of the diene π system would place the C(20) methyl group axial, resulting in allylic strain with the vinyl hydrogen. This mode of cyclization would lead to the undesired product **2.15**. Conversely, an *endo* approach of

the dienophile from the bottom face of the diene pi system would place the C(20) methyl group in an equatorial position. This mode of approach alleviates the steric interaction with the vinyl hydrogen and leads to the desired cycloadduct (–)-**2.4**. Unfortunately, the minor diastereomer could not be isolated in pure form for characterization purposes and was thus tentatively assigned as **2.15**.

## 2-3: Elaboration of the Side Chain Leading to (+)-2.3

### 2-3-1: A Reductive Lithiation Strategy

With bicyclic ester (–)-**2.4** in hand, the next challenge we faced was elaboration of the side chain. The first strategy we explored relied upon a reductive lithiation of a phenyl thioether (Scheme 2.6).[12] Synthesis of the required substrate began with $LiAlH_4$ reduction of (–)-**2.4** and conversion of the resulting alcohol (–)-**2.16** to the corresponding iodide (–)-**2.17** under Appel conditions. Lithiation of thioanisole with *n*-BuLi in the presence of DABCO,[13] followed by addition of (–)-**2.17** resulted in displacement of the iodide to furnish phenyl thioether (–)-**2.18**. Alkyl phenyl sulfides may be reductively cleaved with LiDBB to generate the corresponding alkyllithiums, which can be trapped with various electrophiles.[12,14] We envisioned that reductive lithiation of (–)-**2.18**, followed by trapping with vinylogous triflate **2.19** would constitute an elegant and simple approach to cyclopentenone (–)-**2.20**. While exposure of (–)-**2.18** to LiDBB did successfully generate the desired alkyllithium, this carbanion underwent an unexpected cyclization onto the siloxane, delivering the trans-fused silacyclopentane (–)-**2.21**.



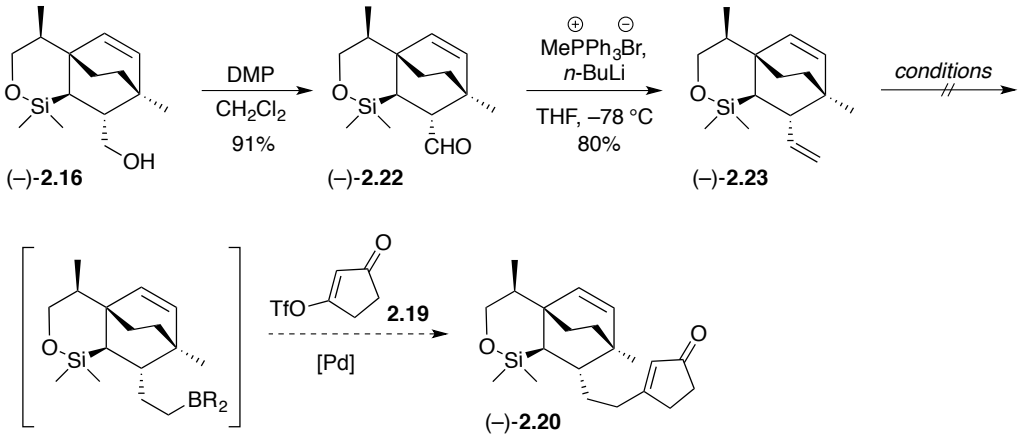

**Scheme 2.6:** Synthesis and Reductive Lithiation of Phenylsulfide (–)-**2.18**

## 2-3-2: A Suzuki Coupling Strategy

Formation of the undesired by-product (–)-**2.21** precluded the generation of a strongly nucleophilic carbanion at C(11) to complete the side chain elaboration. We therefore opted to explore a less nucleophilic intermediate, such as an alkylboron species, that could potentially undergo a *B*-alkyl Suzuki coupling[15] with triflate **2.19**. Hydroboration of the appropriate olefin would provide access to such an intermediate.

To this end, oxidation of alcohol (–)-**2.16** with Dess-Martin periodinane (DMP)[16] provided aldehyde (–)-**2.22** in 91% yield (Scheme 2.7). This aldehyde was found to be extremely unstable, undergoing extensive decomposition within several days even if stored at low temperatures. Subsequent Wittig methylenation under standard conditions ($MePPh_3^+Br^-$, *n*-BuLi, THF, –78 °C) afforded terminal olefin (–)-**2.23** in 80% yield. Unfortunately, this particular olefin was found to be extremely resistant to hydroboration. A variety of different boranes were examined, including 9-BBN and catecholborane with

Wilkinson's catalyst, which led only to the recovery of starting material. Surprisingly, even the relatively small $Et_2BH$ and $Me_2BH$ were ineffective. Increasing the temperature resulted in complex mixtures of products.

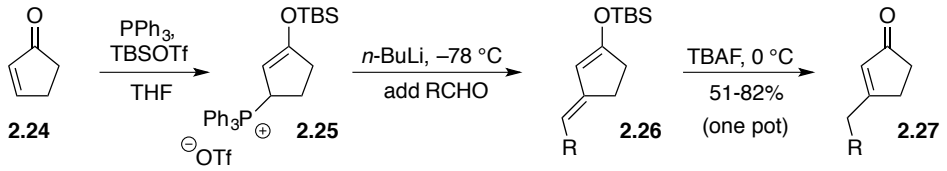



| Entry | Conditions | Result |
|---|---|---|
| 1 | 9-BBN, THF, 25 °C | No reaction |
| 2 | Catecholborane, $(PPh_3)_3RhCl$ THF, 25 °C | No reaction |
| 3 | $Et_2BH$, THF, 25 ° C | No reaction |
| 4 | $Me_2BH$, THF, 25 °C | No reaction |

**Scheme 2.7:** Synthesis and Attempted Hydroboration of Olefin (–)-**2.23**

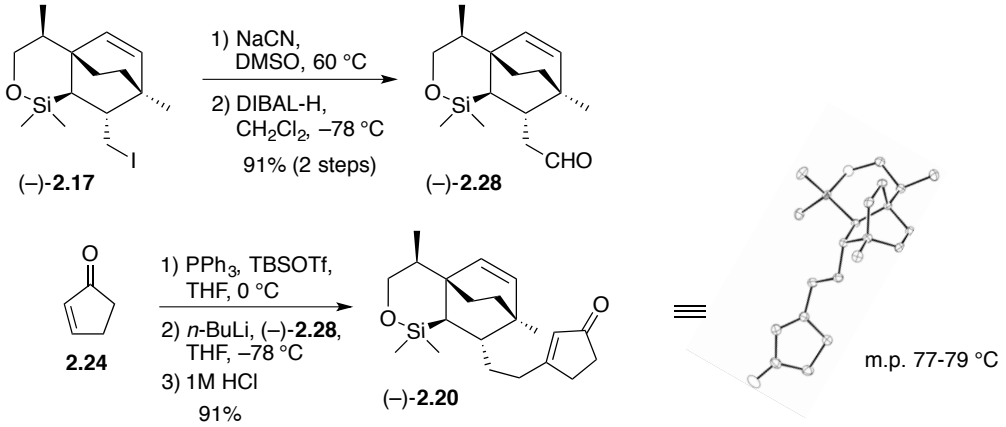
### 2-3-3: Synthesis of Key Intermediate (+)-2.3

An extensive survey of the literature revealed an interesting report by Kozikowski, who employed novel umpolung chemistry to install cyclopentenones (Scheme 2.8).[17] This approach involves conjugate addition of $PPh_3$ to cyclopentenone (**2.24**), followed by trapping of the resulting enolate with TBSOTf to generate the phosphonium salt **2.25**. Deprotonation with *n*-BuLi generated the corresponding ylide, which, when reacted with a variety of aldehydes, furnished silyl dienol ethers (**2.26**). Finally, desilylation with TBAF *in situ* yielded β-susbtituted cyclopentenones (**2.27**).




**Scheme 2.8:** Kozikowski's Umpolung Chemistry

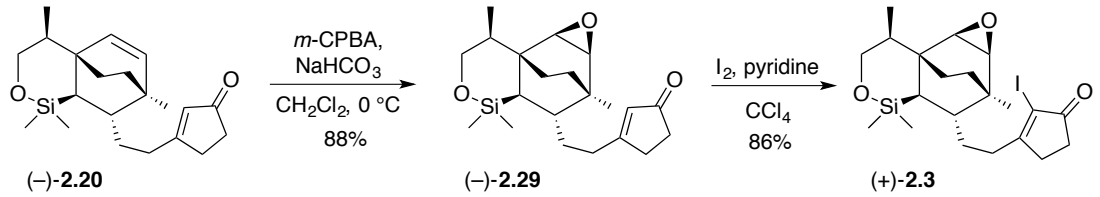
To apply this chemistry in our system, we prepared the homolog of aldehyde (–)-**2.22**. To this end, displacement of the iodide in (–)-**2.17** with NaCN in DMSO, followed by DIBAL–H reduction of the resulting nitrile, afforded aldehyde (–)-**2.28** in 91% yield (2 steps). Gratifyingly, Kozikowski's method proved highly efficient, delivering cyclopentenone (–)-**2.20** as a crystalline solid (m.p. 77-79 °C) in 91% yield (Scheme 2.9). However, we found that 1 M HCl was both more efficient and consistent in the desilylation step. Single crystal X-ray analysis established both the relative and absolute stereochemistry of (–)-**2.20** unambiguously (Scheme 2.9).




**Scheme 2.9:** Synthesis of Cyclopentenone (–)-**2.20**

Treatment of (–)-**2.20** with *m*-CPBA next furnished the desired epoxide (–)-**2.29** as a single diastereomer in 88% yield. Iodination of the cyclopentenone in (–)-**2.29** was then attempted under several conditions, including $TMSN_3/I_2$, NIS, and $I_2$/pyridine. While the

former two conditions led to mixtures of products, Johnson iodination ($I_2$/pyridine/$CCl_4$)[18] cleanly afforded the desired iodide (–)-**2.3** in 86% yield. To ensure complete consumption of starting material and a reasonable reaction time, 6 equivalents of $I_2$ were required (Scheme 2.10).

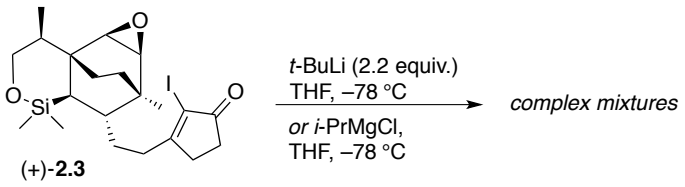



**Scheme 2.10:** Synthesis of Key Intermediate (–)-**2.3**

## 2-4: Studies Directed Towards the Synthesis of Ring D

### 2-4-1: An Epoxide Opening Strategy

Initial cyclization studies involving lithiation of (–)-**2.3** or formation of the Grignard reagent by metal halogen exchange with *i*-PrMgCl led only to complex mixtures of products (Scheme 2.11).




**Scheme 2.11:** Initial Cyclization Studies

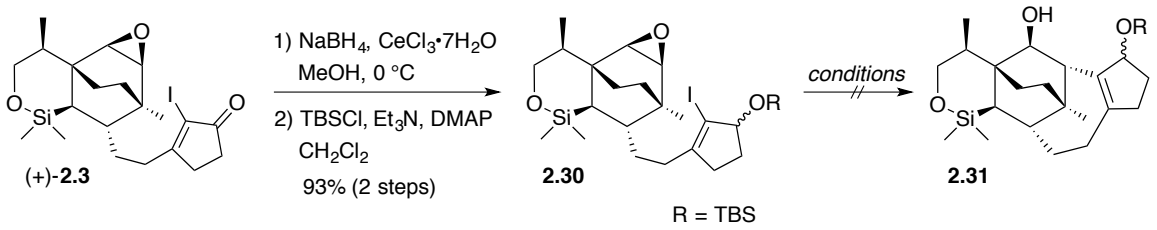
We attributed this problem to be associated with side reactions at the carbonyl group, and decided that a protected secondary hydroxyl, in place of the carbonyl, should mitigate the formation of by-products. To this end, Luche reduction[19] of (–)-**2.3**, followed by protection of the secondary hydroxyl as a TBS ether, furnished **2.30** as a mixture (1:1) of diastereomers for further cyclization studies (Scheme 2.12). Although metal halogen

exchange of iodide **2.30** with *t*-BuLi or *i*-PrMgCl proceeded cleanly, epoxide opening was not observed. More forcing conditions (THF, reflux) resulted in the formation of unidentifiable by-products.

We surmised that the use of Lewis acids might activate the epoxide towards the desired cyclization. A variety of weak Lewis acids such as $ZnCl_2$ and Ti(*i*OPr)$_4$ were investigated, but the only product observed was that resulting from simple metal halogen exchange. Conversion of the vinyllithium species or Grignard reagent derived from **2.30** to their corresponding cuprates, utilizing various copper sources, also failed to bring about the cyclization.

After screening multiple weak Lewis acids, we also attempted the use of strong Lewis acids such as $BF_3$•$OEt_2$ and $TiCl_4$. In each case however, only products arising from skeletal rearrangement were observed. Such rearrangements are common reaction pathways for epoxides situated on bridged bicyclic compounds.[20]

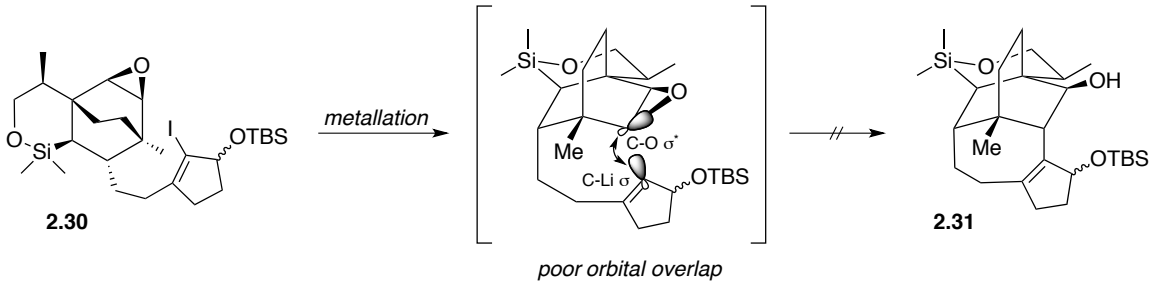
Given the failures associated with epoxide opening by a vinyl carbanion, we questioned whether radical cyclization conditions might prove more fruitful. Typical conditions for generating radicals such as $Bu_3SnH$/AIBN,[21] $Et_3B/O_2$,[22] and $SmI_2$[23] were examined. Unfortunately, these conditions were equally ineffective in bringing about the desired cyclization.




| Entry | Conditions | Result | |
|---|---|---|---|
| 1 | *t*-BuLi, THF, –78 °C → rt | Metal-halogen exchange exclusively | ***Metallation*** |
| 2 | *i*-PrMgCl, THF, –78 °C → rt | Metal-halogen exchange exclusively | |
| 3 | *t*-BuLi, $ZnCl_2$ or $Ti(OiPr)_4$ THF, –78 °C → rt | Metal-halogen exchange exclusively | ***Metallation in the presence of weak Lewis acids*** |
| 4 | *t*-BuLi, CuI or CuBr or CuCN, etc. THF, –78 °C → rt | Metal-halogen exchange exclusively | ***Metallation, then conversion to cuprates*** |
| 5 | *t*-BuLi, $BF_3$•$OEt_2$ or $TiCl_4$ or $Et_2AlCl$ THF, –78 °C | Skeletal rearrangement | ***Metallation in the presence of strong Lewis acids*** |
| 6 | $SmI_2$, THF, rt | Skeletal rearrangement | |
| 7 | $Bu_3SnH$, AIBN toluene, reflux | Complex mixture | ***Radical cyclization conditions*** |

**Scheme 2.12:** Attempted Cyclization of Epoxide **2.30**

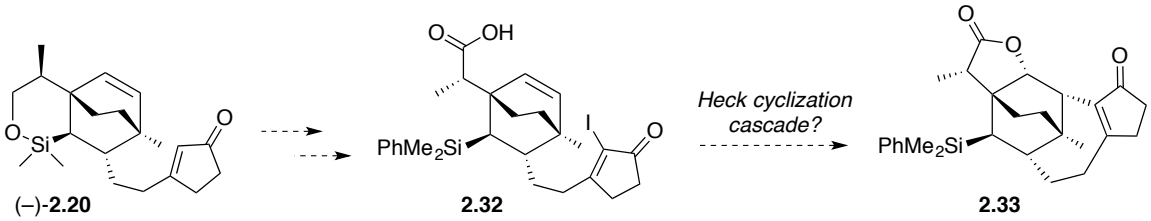
The failure of **2.30** to undergo the desired cyclization is likely due to stereoelectronic effects. For the epoxide opening to occur, overlap of the σ orbital of the nucleophile with the C-O antibonding (σ*) orbital would be necessary in the transition state. The rigidity of the bicyclic system prevents the attainment of such overlap (Scheme 2.13).




**Scheme 2.13.** Hypothesis for the Failure of **2.30** to Undergo Cyclization

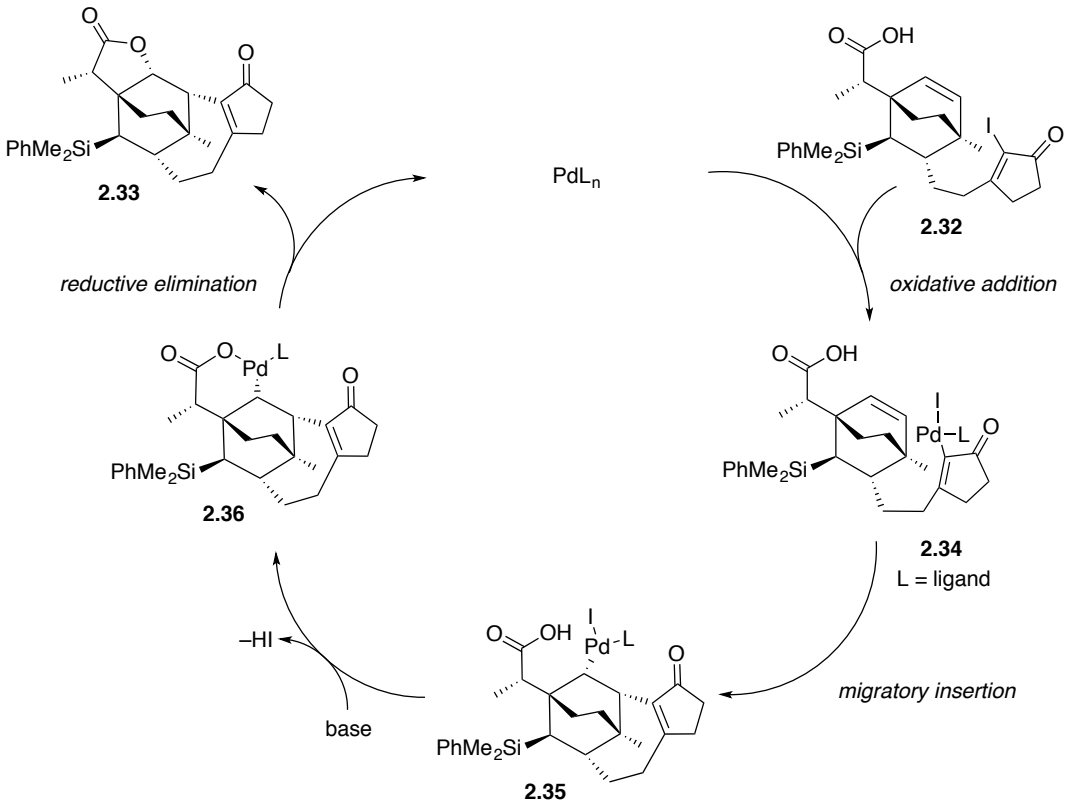
### 2-4-2: A Heck Cyclization Cascade Strategy

Convinced that the transannular epoxide opening was not a viable strategy to access the D ring, we opted to revise our original approach. Earlier studies had revealed that the siloxane ring in these substrates was subject to nucleophilic opening by phenyllithium. We envisioned access to substrate **2.32**, bearing a vinyl iodide and a pendant nucleophile (carboxylic acid), that could potentially undergo a Heck cyclization cascade[24] to furnish lactone **2.33** (Scheme 2.14).




**Scheme 2.14:** Proposed Synthesis of the D Ring via a Heck Cyclization Cascade

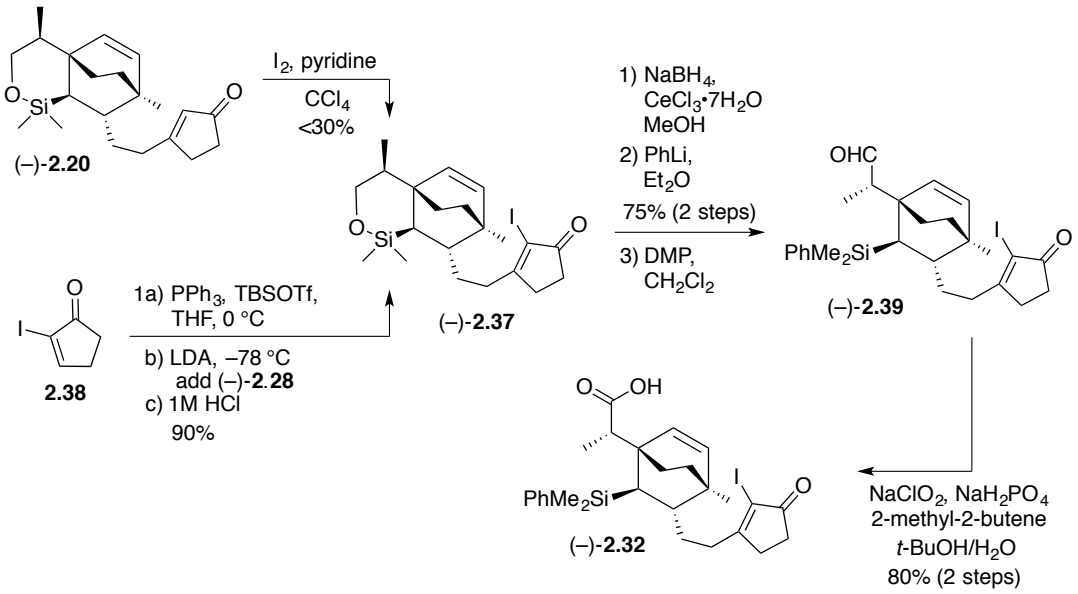
Mechanistically (Scheme 2.15), the proposed cascade reaction involves initial oxidative addition of $Pd^0$ into the vinyl iodide bond of **2.32**, resulting in the vinyl palladium intermediate **2.34**. Migratory insertion into the olefin would give an alkylpalladium species (**2.35**) that is incapable of β-hydride elimination, due to the lack of *syn*-β hydrogens. Therefore, the palladium center would be subject to nucleophilic attack by the carboxyl group to generate palladacycle **2.36**. Finally, reductive elimination would deliver lactone **2.33** and regenerate the palladium catalyst.




**Scheme 2.15:** Mechanistic Proposal for the Heck Cyclization Cascade

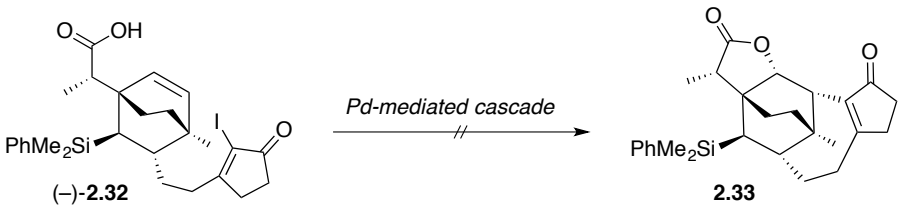
The synthesis of **2.32** first required iodination of enone (–)-**2.20**. Contrary to (–)-**2.29**, bearing an epoxide in place of the olefin, iodination of (–)-**2.20** proceeded in very low yields and was accompanied by the formation of substantial amounts of tar, which made the workup and purification very difficult. We reasoned it should be possible to access iodide **2.37** from aldehyde (–)-**2.28** employing a modification of the Kozikowski chemistry[17] (Scheme **2.8**). By utilizing 2-iodocyclopentenone (**2.38**) and LDA as the base (instead of *n*-BuLi) to avoid metal-halogen exchange, vinyl iodide (–)-**2.37** was indeed obtained directly from aldehyde (–)-**2.28** in 90% yield (Scheme 2.16). Ketalization of the carbonyl in (–)-**2.37** was found to be quite difficult. Therefore, a Luche reduction[19] was used to protect this moiety from phenyllithium, which was used in the subsequent step to

open the siloxane ring. Exposure of the resulting diol to excess DMP then afforded aldehyde (–)-**2.39**. Finally, Pinnick oxidation[25] provided the requisite intermediate (–)-**2.32** for the Heck cyclization studies.




**Scheme 2.16:** Synthesis of Heck Cyclization Precursor (–)-**2.32**

A wide variety of conditions were explored to bring about the cascade cyclization (Scheme 2.17). These conditions involved the use of various sources of $Pd^0$ or $Pd^{II}$, diverse ligands, and several different bases. In many cases, only the product resulting from proto-dehalogenation was observed. The other conditions that we surveyed either led to the recovery of starting material or decomposition of the substrate.




| Entry | Conditions | Result |
|---|---|---|
| **1** | $Pd_2(dba)_3$, P(*o*-tol)$_3$, $Et_3N$ MeCN, reflux | Unidentifiable by-product |
| **2** | $Pd(PPh_3)_4$, P(*o*-tol)$_3$, $Et_3N$ toluene, 80 °C | Decomposed |
| **3** | $Pd(cy_3P)_2$, $NaHCO_3$, THF, reflux | No reaction |
| **4** | $Pd_2(dba)_3$, (2-furyl)$_3$P, $NaHCO_3$ THF, reflux | Dehalogenation |
| **5** | $Pd_2(dba)_3$, (*p*-$C_6H_4F$)$_3$P, $NaHCO_3$, THF, reflux | Mainly SM |
| **6** | $Pd_2(dba)_3$, $PPh_3$, $Et_3N$ MeCN, 60 °C | Decomposed |
| **7** | $Pd_2(dba)_3$, dppe, $Et_3N$ MeCN, 60 °C | Decomposed |
| **8** | $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, $NaHCO_3$, toluene, reflux | Complex mixture |
| **9** | $Pd(PPh_3)_4$, $PBu_3$, $Cs_2CO_3$ toluene, reflux | Unidentifiable by-product (no indication of **2.33**) |

**Scheme 2.17:** Attempted Synthesis of Lactone **2.33** via a Heck Cyclization Cascade

After extensive screening of conditions, we became convinced that the proposed Heck cyclization cascade would not be a viable strategy for moving forward. Several other approaches were briefly investigated, but proved to be similarly fruitless, and the D ring continued to remain elusive.

## 2-5: References


1. (a) Mitsunobu, O. *Synthesis* **1981**, 1-28. (b) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380-&.

2. (a) Tamao, K. *J. Syn. Org. Chem. Jpn.* **1988**, *46*, 861-878. (b) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694-1696.

3. (a) Roush, W. R. *J. Am. Chem. Soc.* **1978**, *100*, 3599-3601. (b) Roush, W. R., in "*Comprehensive Organic Synthesis*" (Trost, B. M.; Fleming, I., eds.), Pergamon Press: Oxford, 1991, vol. 5, pp. 551-593.

4. Takeshita, K.; Seki, Y.; Kawamoto, K.; Murai, S.; Sonoda, N. *J. Org. Chem.* **1987**, *52*, 4864-4868.

5. Yadav, J. S.; Basak, A. K.; Srihari, P. *Tetrahedron Lett.* **2007**, *48*, 2841-2843.

6. Mori, K. *Tetrahedron:Asymmetry* **2005**, *16*, 1721-1721.

7. Prashad, M.; Har, D.; Kim, H. Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067-7070.

8. Birch, A. J. *J. Chem. Soc.* **1944**, 430-436.

9. Pearson, D. E.; Buehler, C. A. *Chem. Rev.* **1974**, *74*, 45-86.

10. Sieburth, S. M.; Lang, J. *J. Org. Chem.* **1999**, *64*, 1780-1781.

11. Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed.* **1980**, *19*, 779-807.

12. (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924-1930. (b) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064-1071.

13. Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097-4099.

14. Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152-161.

15. Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544-4568.

16. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.

17. Kozikowski, A. P.; Jung, S. H. *J. Org. Chem.* **1986**, *51*, 3400-3402.

18. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1992**, *33*, 917-918.

19. Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.

20. (a) Berson, J. A., in *"Molecular Rearrangements*" (De Mayo, P., ed.), Wiley: New York, 1963, vol. 1, pp. 111-231. (b) Pocker, Y., in *"Molecular Rearrangements*" (De Mayo, P., ed.), Wiley: New York, 1963, vol. 1, pp. 1-25.

21. Kuivila, H. G. *Synthesis* **1970**, 499-509.

22. Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415-3434.

23. Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37*, 175-180.

24. (a) Kucera, D. J.; Oconnor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304-5306. (b) Fox, M. E.; Li, C.; Marino, J. P.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467-5480. (c) Hong, C. Y.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 3453-3456.

25. (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888-890. (b) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091-2096.

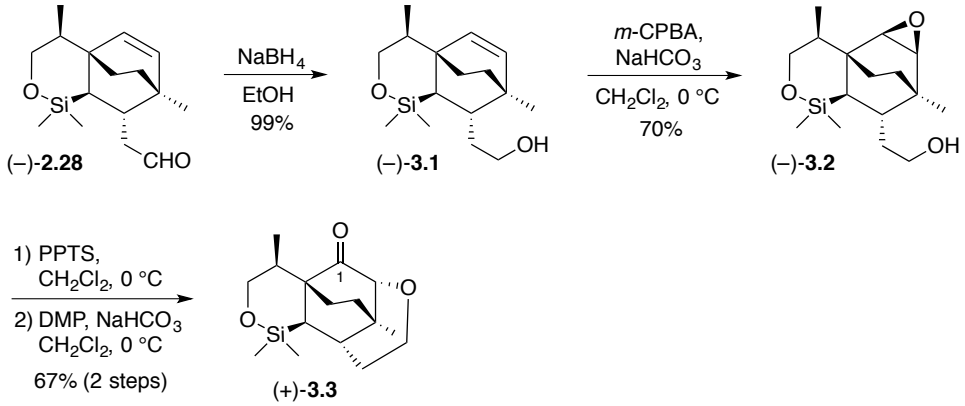
# CHAPTER 3

# A Revised Synthetic Approach

## 3-1: Regioselective Installation of the C(1) Carbonyl

Failure to secure the D ring of (–)-calyciphylline N by the various approaches discussed in Chapter 2 convinced us that a significant revision of the synthetic strategy was required. We questioned whether or not the epoxide functionality could be opened intramolecularly by a pendant hydroxyl group, as this would provide a means to install the C(1) carbonyl, potentially a valuable functional handle for further elaboration.

To test this hypothesis, reduction of aldehyde (–)-**2.28** with $NaBH_4$ in MeOH and subsequent epoxidation of (–)-**3.1** with *m*-CPBA afforded epoxy alcohol (–)-**3.2** as a single diastereomer. Pleasingly, exposure of (–)-**3.2** to a catalytic amount of PPTS in $CH_2Cl_2$ at 0 °C resulted in rapid cyclization. Dess Martin oxidation of the crude mixture facilitated purification, providing ketone (+)-**3.3** in 67% yield over the two steps.

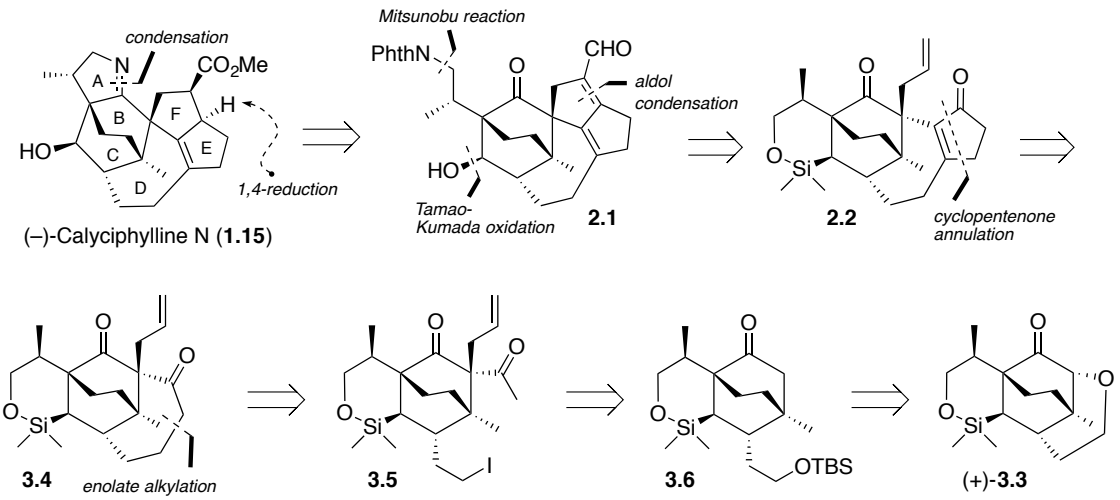



**Scheme 3.1:** Installation of the C(1) Carbonyl Group

Our ability to access ketone (+)-**3.3** now set the stage for the development of a new synthetic strategy.

## 3-2: A Second Generation Retrosynthetic Analysis

Our revised retrosynthetic analysis is outlined in Scheme 3.2. Several disconnections remain unchanged from the initial synthetic plan (Scheme 2.1), but diverge at intermediate **2.2**. Thus, the E ring would be constructed at a later stage through a cyclopentenone annulation, simplifying the structure to diketone **3.4**. The D ring was now envisioned to arise via an intramolecular enolate alkylation of iodide **3.5**, which in turn could be assembled through elaboration of ketone **3.6**. Finally, **3.6** could be accessed after reductive cleavage of tetrahydropyran (+)-**3.3**.

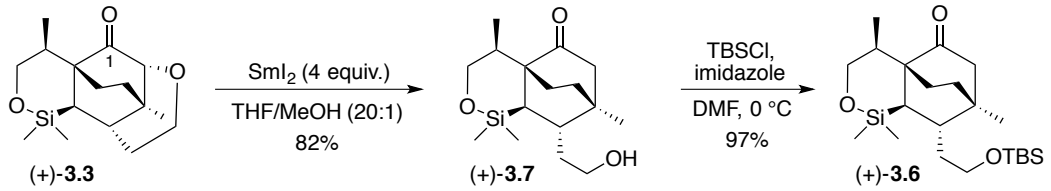



**Scheme 3.2:** Revised Retrosynthetic Analysis

## 3-3: Synthesis of Diketone (+)-3.4

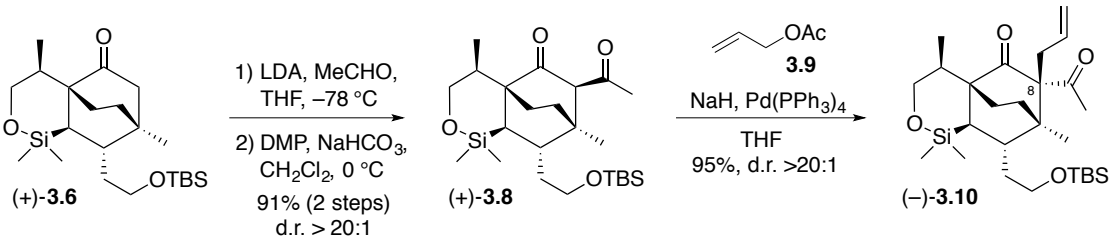
After a brief survey of reaction conditions, we discovered that 4 equivalents of $SmI_2$ in a solution of THF/MeOH smoothly promoted reductive cleavage[1] of the tetrahydro-pyran ring in (+)-**3.3** to provide crystalline hydroxy ketone (+)-**3.7** in 82% yield (Scheme 3.3). Methanol was an essential additive, as rapid protonation of the intermediate enolate was necessary to avoid side reactions. Furthermore, quenching of the reaction under

different conditions gave widely different results. While a 1 M HCl quench resulted in formation of unidentifiable by-products, pouring the reaction mixture into saturated $NaHCO_3$ gave consistently high yields of (+)-**3.7**. Protection of the primary hydroxyl then provided TBS ether (+)-**3.6** in 97% yield.



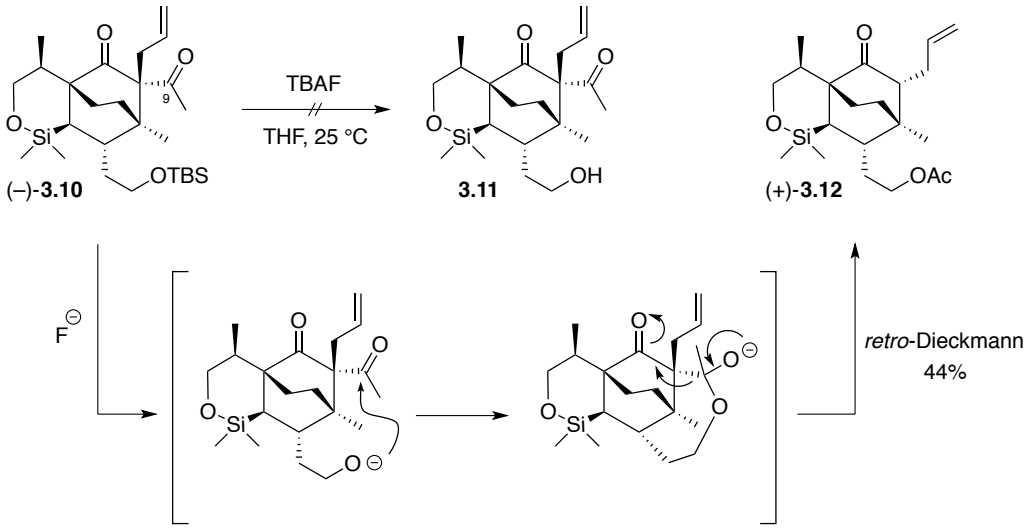

**Scheme 3.3:** Reductive Cleavage of Tetrahydropyran (+)-**3.3**

Next, we explored the installation of the C(8) quaternary center. Not surprisingly, direct acylation of the sterically hindered carbonyl in (+)-**3.6** was found to be quite difficult. The lithium enolate, with or without added HMPA, failed to react with $Ac_2O$, EtOAc, and 1-acetyl imidazole. The sodium and potassium enolates were found to be similarly unreactive. Fortunately, an aldol reaction with acetaldehyde, followed by oxidation of the resulting β-hydroxy ketone (DMP), an effective protocol reported in 1981 by Smith and Levenberg for the construction of 1,3-dicarbonyl compounds,[2] led to diketone (+)-**3.8** in 91% yield over 2 steps (Scheme 3.4). While treatment of (+)-**3.8** under basic conditions with allyl bromide gave complex mixtures of products, a Tsuji-Trost allylation[3] with allyl acetate (**3.9**), NaH, and catalytic $Pd(PPh_3)_4$ (5 mol%) in THF furnished the desired product (–)-**3.10** as a single diastereomer in 95% yield.




**Scheme 3.4:** Installation of the C(8) Quaternary Center

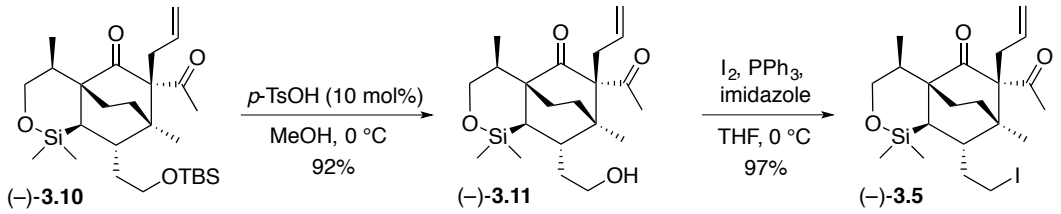
Interestingly, when deprotection of the TBS ether in (–)-**3.10** was attempted with TBAF, none of the desired alcohol **3.11** was obtained. Instead, the major product isolated from the reaction mixture was identified as acetate (+)-**3.12** (Scheme 3.5). Mechanistically, this product arises from intramolecular attack of the intermediary alkoxide onto the C(9) carbonyl, followed by a *retro*-Dieckmann reaction. Notably, this result proves that the correct stereochemistry at C(8) had been established in the allylation step.




**Scheme 3.5:** Undesired Retro-Dieckmann Pathway

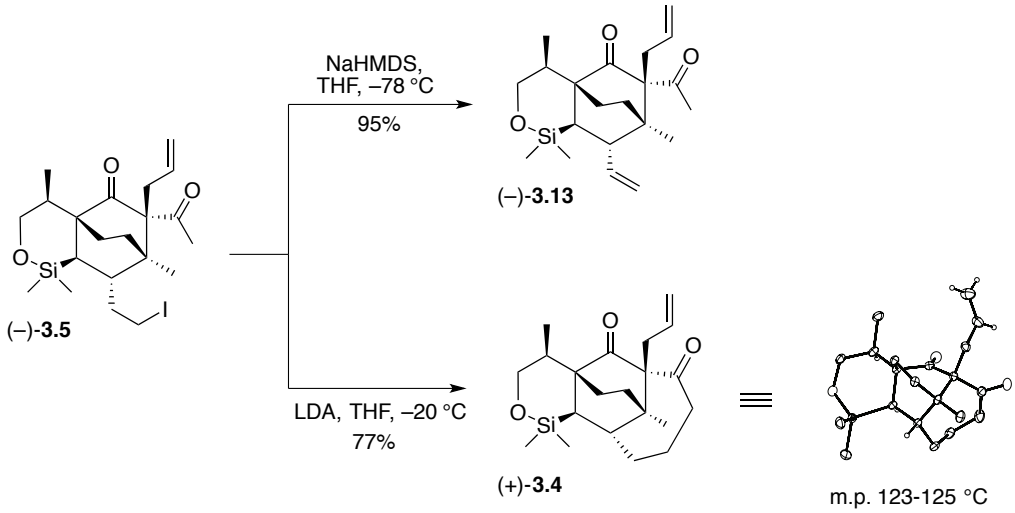
Since an alkoxide was identified as the culprit in this undesired side reaction, we surmised that deprotection of the TBS ether under acidic conditions would eliminate this reaction pathway. Indeed, exposure of (–)-**3.10** to catalytic *p*-TsOH in MeOH provided (–)-**3.11** in 92% yield (Scheme 3.6). Alcohol (–)-**3.11** revealed such a propensity to

undergo the undesired retro-Dieckmann pathway that even quenching of the reaction mixture with saturated aqueous $NaHCO_3$ resulted in the formation of only the by-product (+)-**3.12**. Therefore a simple aqueous wash to remove *p*-TsOH was employed in the workup. Conversion of the alcohol to the corresponding iodide was then accomplished without incident to afford the key cyclization precursor (–)-**3.5** in 97% yield.




**Scheme 3.6:** Synthesis of Iodide (–)-**3.5**

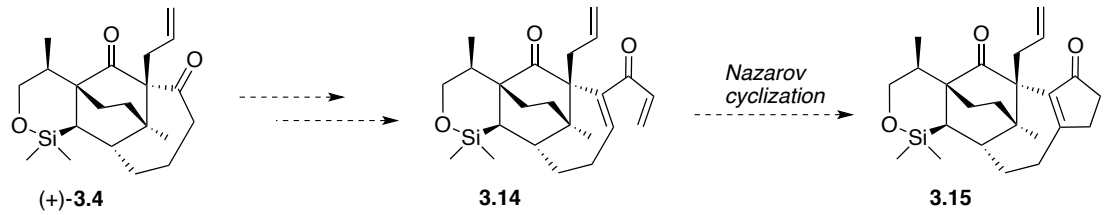
We were delighted to find that dropwise addition of LDA to a solution of the iodoketone in THF at –20 °C provided tetracycle (+)-**3.4** as a crystalline solid (m.p. 123-125 °C) in 77% yield (Scheme 3.7). Single crystal X-ray analysis confirmed the structure, as well as the relative and absolute stereochemical configurations. Interestingly, treatment of (–)-**3.5** with NaHMDS gave only the elimination product (–)-**3.13**.




**Scheme 3.7:** Completion of the D Ring

## 3-4: Construction of Ring E

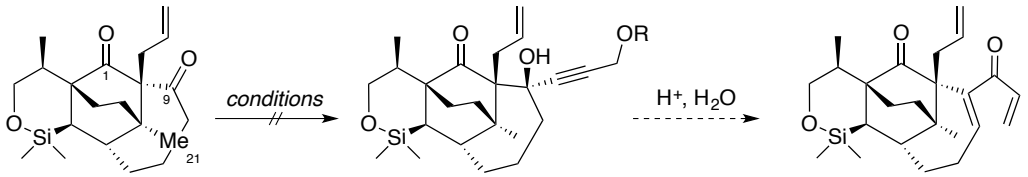
With the D ring secured, we next turned our attention to elaboration of the eastern hemisphere. For the planned cyclopentenone annulation to construct ring E, we envisioned the advancement of (+)-**3.4** to a substrate bearing a divinyl carbonyl moiety such as **3.14**. Nazarov cyclization[4] of **3.14** would then permit access to cyclopentenone **3.15**.



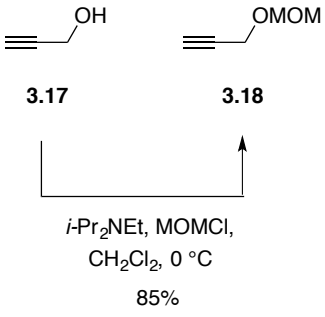

**Scheme 3.2:** General Strategy Towards Construction of Ring E

### 3-4-1: A Tandem Rupe Rearrangement/Nazarov Cyclization Strategy

One method of accessing divinyl ketones relies upon the acid catalyzed isomerization of 1,4-butyne diols (Rupe rearrangement[5]/dehydration sequence). Under the reaction conditions, these intermediates typically undergo the Nazarov cyclization *in situ*. Pursuant to this strategy, we attempted to add the acetylide anion derived from propargyl alcohol (or an O–protected propargyl alcohol) to ketone (+)-**3.4**. Reaction with the fully substituted C(1) carbonyl was not considered as a possibility on steric grounds. Unfortunately, the C(9) carbonyl was found to be similarly unreactive. Neither the lithium acetylide, the Grignard reagent, nor the cerium acetylide was successful in providing the desired 1,4-butynediol **3.16**, even under forcing conditions (Scheme 3.9). Inspection of molecular models suggested that the Dunitz-Bürgi linear trajectory is blocked from the bottom face by the concavity of the ring system, and blocked from the top face by the presence of the C(21) methyl group.



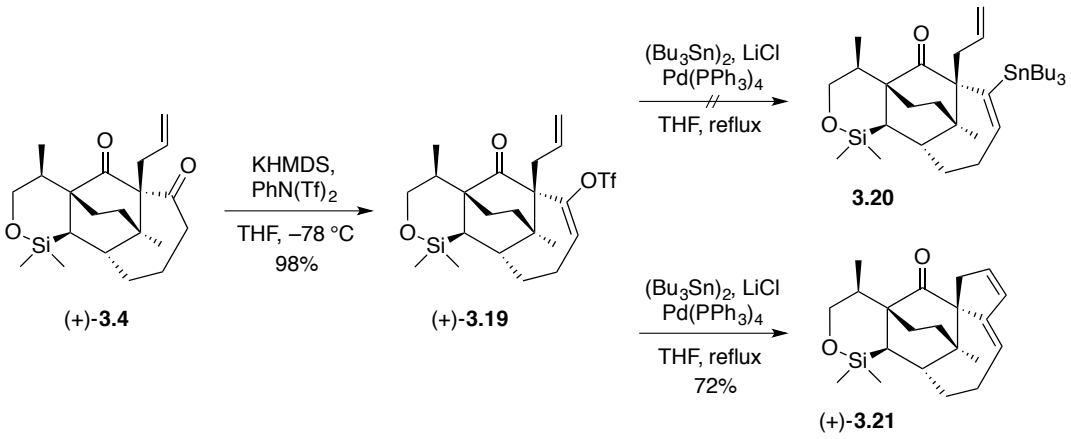

| Entry | Condtions | Result |
|---|---|---|
| 1 | **3.17**, *n*-BuLi (2 equiv.) THF, –78 °C → rt | No reaction |
| 2 | **3.17**, EtMgBr (2 equiv.), THF, rt → reflux | No reaction |
| 3 | **3.18**, *n*-BuLi, HMPA, THF, –78 °C → rt | No reaction |
| 4 | **3.18**, KOtBu, DMSO | Complex mixture |
| 5 | **3.18**, *n*-BuLi, $CeCl_3$, THF, –78 °C → rt | No reaction |




**Scheme 3.3:** Attempted Acetylide Addition to Ketone (+)-**3.4**

### 3-4-2: A Stille Coupling Strategy

We next explored the possibility of converting ketone (+)-**3.4** to the corresponding vinyl tributylstannane, which we anticipated could undergo a Stille coupling[6] with acryloyl chloride to access **3.14**. To this end, enolization of (+)-**3.4** with KHMDS in the presence of $PhN(Tf)_2$ at –78 °C afforded vinyl triflate (+)-**3.19** in 98% yield (Scheme 3.10). We next attempted to install the vinyl tributylstannane via cross coupling of (+)-**3.19** with $(Bu_3Sn)_2$ and catalytic $Pd(PPh_3)_4$ (5 mol%). However, the desired stannane **3.20** was not observed, because (+)-**3.19** simply underwent an intramolecular Heck reaction[7] with the pendant allyl group to furnish (+)-**3.21** as the major product.

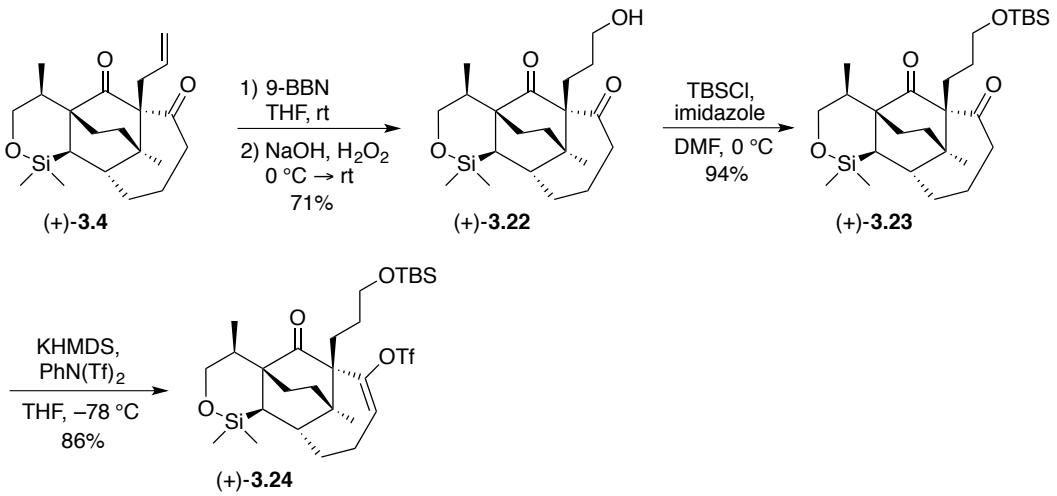



**Scheme 3.10:** Undesired Heck Cylization of Triflate (+)-**3.19**

### 3-4-3: Synthesis of Ring E Utilizing a Stille Carbonylative Cross Coupling Reaction

Another method for the construction of divinyl ketones is via the Stille carbonylative cross coupling.[8] Before exploring this strategy in our system, we were aware that we would have to functionalize the pendant allyl group first, in order to eliminate the possibility of the Heck cyclization pathway (Scheme 3.10).

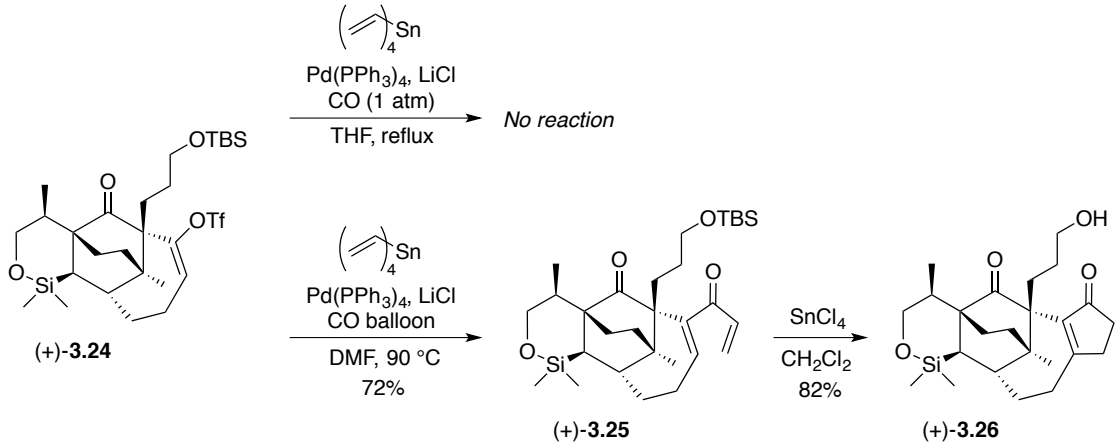
To this end, hydroboration of (+)-**3.4** with 9-BBN,[9] followed by oxidation of the resulting organoborane (NaOH and $H_2O_2$) afforded the expected alcohol (+)-**3.22** in 71% yield (Scheme 3.11). Protection of the alcohol provided TBS ether (+)-**3.23**, which was converted to vinyl triflate (+)-**3.24** in excellent yield (86%) under the previously established conditions (KHMDS, $PhN(Tf)_2$, THF, 78 °C). Excess $PhN(Tf)_2$ was extremely difficult to remove from the product, with some remaining even after chromatography. Furthermore, the reaction had to be quenched very carefully with pH 7 buffer at –78 °C to avoid varying amounts of triflate hydrolysis during the workup.




**Scheme 3.11:** Synthesis of Vinyl Triflate (+)-**3.24**

With the functionalized vinyl triflate (+)-**3.24** in hand, the stage was now set to explore the proposed Stille carbonylation. We quickly discovered that while no reaction occurred in THF at reflux, heating a DMF solution of (+)-**3.24**, LiCl, tetravinyltin, and catalytic $Pd(PPh_3)_4$ (5 mol%) at 90 °C under balloon pressure of CO afforded the requisite divinyl ketone (+)-**3.25** in 72% yield (Scheme 3.12). Despite a clean reaction profile (TLC, crude $^1$H NMR), silica gel chromatography consistently provided very low isolated yields of (+)-**3.25** (<30%). Deactivation of the silica gel with $Et_3N$ failed to improve the yields. However, (+)-**3.25** could be purified in good isolated yields by employing MPLC. Presumably, the large number of purifications carried out on this column had substantially deactivated the silica gel, thus allowing very sensitive compounds to be purified efficiently. Despite the harsh conditions typically required for Nazarov cyclizations (excess protic or Lewis acids, high temperatures), we were delighted to find that exposure of (+)-**3.25** to $SnCl_4$ in $CH_2Cl_2$ at ambient temperature readily led to the cyclization with concomitant removal of the TBS group to furnish cyclopentenone (+)-**3.26** in 82% yield. While a variety of other Lewis acids ($BF_3$•$OEt_2$,

$FeCl_3$, etc.) were also effective for promoting this reaction, $SnCl_4$ tended to give the most consistent results.

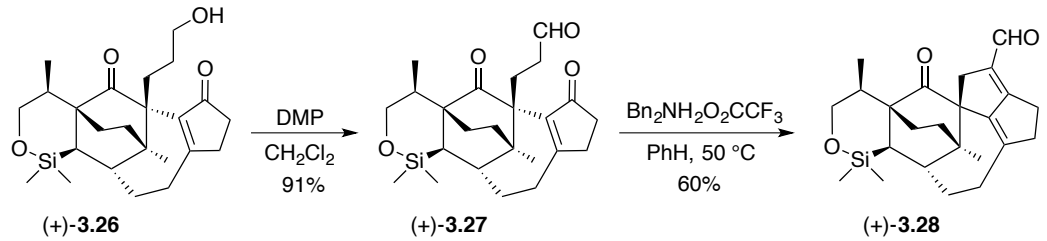



**Scheme 3.12:** Completion of the E Ring

## 3-5: Studies Towards the Construction of Ring F

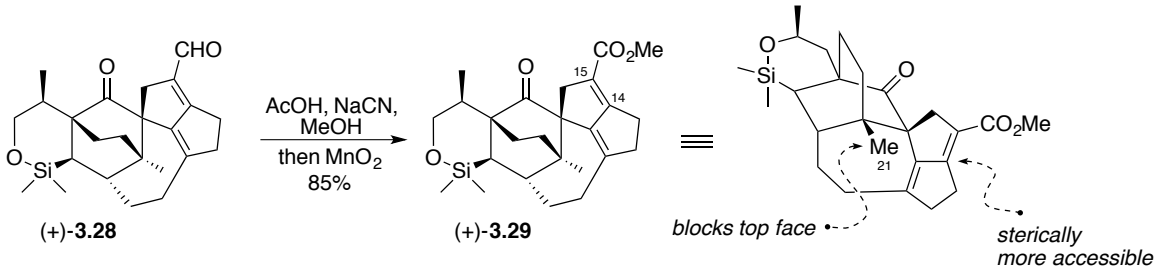
### 3-5-1: Synthesis and Attempted Conjugate Reduction of Unsaturated Ester (+)-3.29

Having found an efficient strategy for the construction of ring E, we next turned our attention towards elaboration of ring F. To this end, oxidation of (+)-**3.26** provided aldehyde (+)-**3.27** in 91% yield (Scheme 3.13). The critical aldol condensation to prepare unsaturated aldehyde (+)-**3.28** was brought about employing the conditions reported by Carreira and Weiss ($Bn_2NH_2O_2CCF_3$, PhH, 50 °C)[10] for a similar ring system en route to (+)-daphmanidin E (Scheme 1.10).




**Scheme 3.13:** Aldol Condensation Leading to Aldehyde (+)-**3.28**

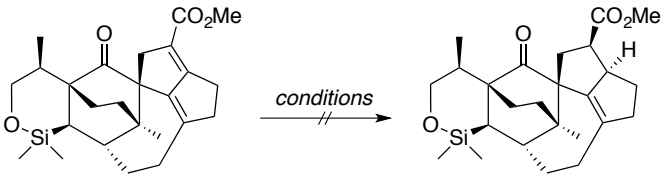
Oxidation of (+)-**3.28** to the corresponding methyl ester (+)-**3.29** was readily achieved in 85% yield utilizing Corey's conditions (AcOH, NaCN, $MnO_2$, MeOH).[11] At this point, the last major hurdle to overcome towards completion of the EF ring system was reduction of the α,β-olefin to set the stereochemistry at C(14) and C(15) (Scheme 3.14). We were cognizant of the challenges associated with this task, specifically, that the olefin to be reduced was tetrasubstituted and in a sterically hindered environment. Moreover, chemoselectivity (1,4- vs. 1,6-reduction), as well as diastereoselectivity (facial selectivity of the reduction) were major concerns. However, inspection of molecular models suggested the following; that the γ, δ–olefin was more sterically encumbered than the α, β–olefin, and that the C(21) methyl group appears to block top facial approach such that the reduction should occur with the desired facial selectivity.




**Scheme 3.14:** Synthesis and Conformational Analysis of (+)-**3.29**

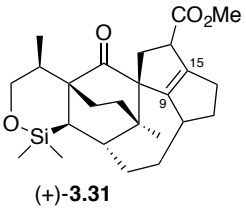
A wide variety of conditions for the reduction of (+)-**3.29** were explored (Scheme 3.15). Stryker's reagent was ineffective, as was the DIBAL-H/CuI/HMPA protocol. Rhodium catalyzed hydrosilylations (Wilkinson's catalyst or $RhCl_3$ with $Et_3SiH$) resulted only in the recovery of starting material, while $Li/NH_3$ reduction gave an intractable mixture of products. Attempted heterogeneous hydrogenations ($PtO_2$ or Pd/C) under pressures as high as 1000 psi also proved unsuccessful. An interesting result was obtained during hydrogenation of (+)-**3.29** with Crabtree's catalyst.[12] At 1 atm of $H_2$ pressure, no

reaction occurred, while a single new product with the correct mass ($M^{+1}$ = 429) was produced upon hydrogenation at 400 psi. Disappointingly, careful analysis of the 2D NMR data including TOCSY, HMBC, and HSQC revealed saturated ester (+)-**3.31** to be the product, wherein the hydrogenation was accompanied by isomerization of the remaining olefin to the undesired C(9)-C(15) position. Upon concluding the incorrect regiochemistry of the olefin resulted, we did not perform a NOESY analysis.

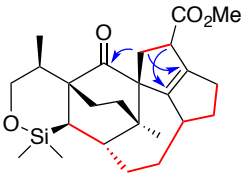



(+)-**3.29** **3.30**

| Entry | Conditions | Result |
|---|---|---|
| **1** | $[(Ph_3P)CuH]_6$, toluene | No reaction |
| **2** | $H_2$ (400 psi), $[(COD)(py)(PCy_3)]IrPF_6$ $CH_2Cl_2$, 25 °C | (+)-**3.31**, 79% |
| **3** | $Li/NH_3$, THF/MeOH (1:2), –78 °C | Complex mixture |
| **4** | $SmI_2$, THF/MeOH | No reaction |
| **5** | $SmI_2$, HMPA, THF/MeOH | No reaction |
| **6** | $H_2$ (1 atm), $[(COD)(py)(PCy_3)]IrPF_6$ $CH_2Cl_2$, 25 °C | No reaction |
| **7** | $RhCl_3$, $Et_3SiH$ benzene, reflux | No reaction |
| **8** | $(Ph_3P)_3RhCl$, $Et_3SiH$, benzene, reflux | No reaction |



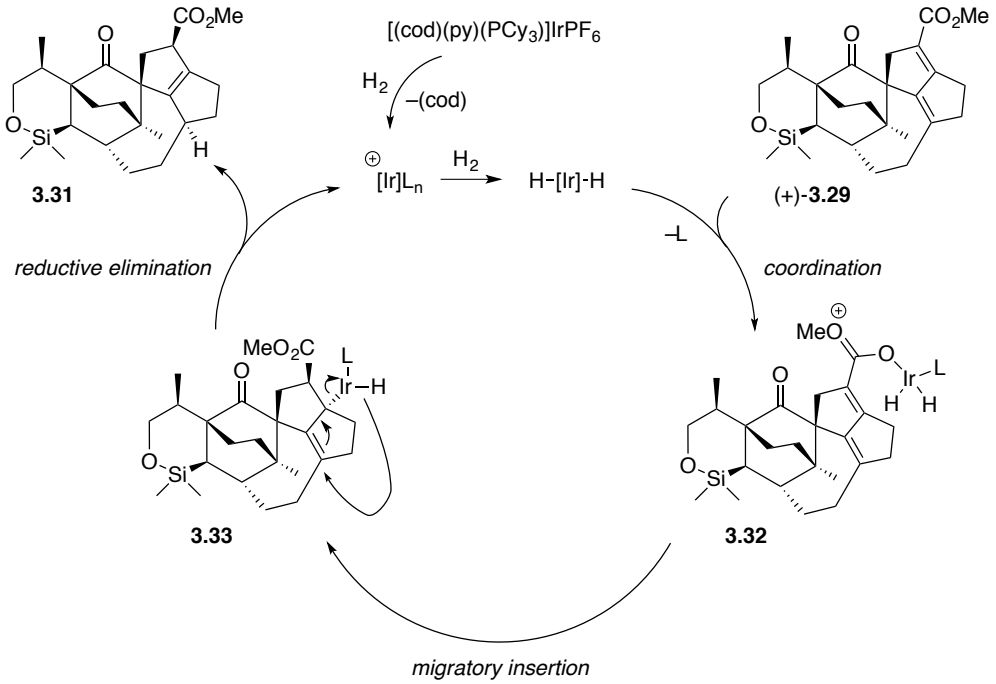

(+)-**3.31**




Selected HMBC Correlations
Selected TOCSY Correlations

**Scheme 3.15:** Attempted Reduction of the α,β-Olefin in (+)-**3.29**

One possible explanation for the formation of (+)-**3.31** involves the initial coordination of the iridium catalyst to the ester carbonyl (Scheme 3.16). Migratory insertion of the iridium dihydride species would give an allylic iridium intermediate **3.33**. Reductive elimination through a 1,4-hydride transfer mechanism would then lead to the observed product (+)-**3.31**.



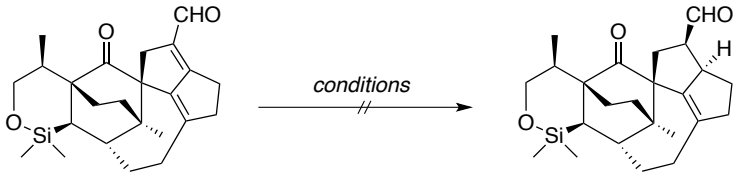

**Scheme 3.16:** Hypothesis for the Formation of Mono-unsaturated Ester (+)-**3.31**

Alternatively, the desired product **3.30** may be formed as an intermediate; subsequent reinsertion of the H-Ir–H complex followed by β-hydride elimination would then result in isomerization of the remaining olefin.

### 3-5-2: Conjugate Reduction of Unsaturated Aldehyde (+)-3.28

An extensive survey of the literature revealed a variety of conjugate reduction conditions that were suitable for unsaturated aldehydes, but not esters. Thus, given the difficulties with the 1,4-reduction of unsaturated ester (+)-**3.29**, we opted to investigate the 1,4-reduction of the corresponding aldehyde (+)-**3.28**. Many conditions for this reduction were explored (Scheme 3.17). Heterogeneous hydrogenation was still ineffective, as were a variety of CuH methods. Not surprisingly, several conditions

resulted in 1,2-reduction of the aldehyde, including rhodium and copper catalyzed hydrosilylations.



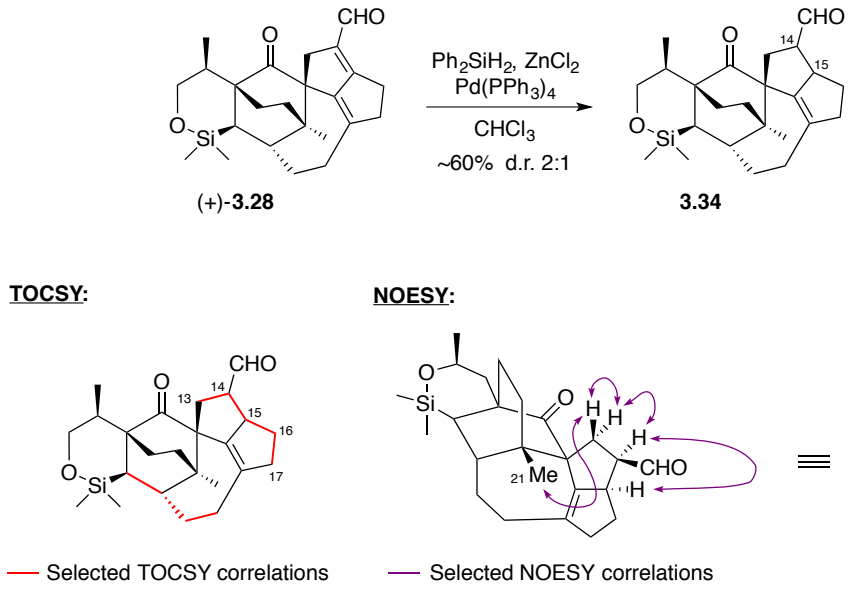

(+)-**3.28** **3.34**

| Entry | Conditions | Result |
|---|---|---|
| 1 | $Et_3SiH$, $(PPh_3)_3RhCl$<br>Benzene, 60 °C | 1,2-reduction |
| 2 | TMSCl, MeLi, CuI, DIBAL-H<br>THF, HMPA, –50°C → rt | No reaction |
| 3 | $Ph_2SiH_2$, [Cu], NaO*t*Bu<br>toluene | 1,2-reduction |
| 4 | $H_2$ (1 atm), Pd/C<br>EtOAc | No reaction |
| 5 | $H_2$ (100 psi - 1000 psi), Pd/C<br>EtOAc or MeOH | No reaction |
| 6 | $Rh(COD)_2BF_4$, $Zn(OTf)_2$, $H_2$ (400 psi)<br>MeOH/EtOAc, 70 °C | Complex mixture |

**Scheme 3.17:** Attempted Conjugate Reduction of Unsaturated Aldehyde (+)-**3.28**

Finally, a set of conditions [$Pd(PPh_3)_4$, $ZnCl_2$, $Ph_2SiH_2$][13] was identified that provided a mixture of diastereomers (2:1) with the correct mass (Scheme 3.18). The major diastereomer could be isolated by silica gel chromatography. Several 2D NMR experiments were then performed. Inspection of the TOCSY NMR revealed interrupted coupling of the hydrogens at C(13) to C(17), indicating that the highlighted regions were isolated spin systems, thus confirming that 1,4- as opposed to 1,6-reduction had occurred, and importantly, without concomitant isomerization of the remaining olefin. With the correct regiochemistry established, a NOESY spectrum was obtained to determine the stereochemistry at C(14) and C(15). The most important nOe correlations were the

following: H(21) to H(13α), H(13α) to H(13β), H(13β) to H(14), H(14) to H(15), and H(21) to the aldehyde C*H*O. On the basis of this analysis, the structure of the major product could be assigned as **3.34**.




**Scheme 3.18:** Successful 1,4-Reduction of Unsaturated Aldehyde (+)-**3.28**; TOCSY and NOESY Correlations Leading to the Assignment of the Major Diastereomer

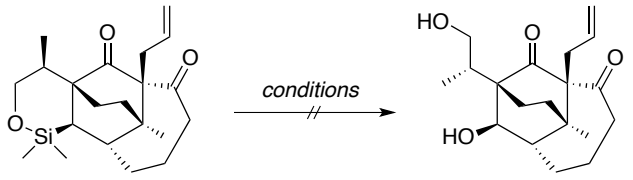
While the yield and diastereoselectivity for the reduction were certainly not ideal, we planned to optimize this reaction at a later stage, towards the very end of the synthesis. Moreover, the reaction was not clean and **3.34** could not be isolated in reasonable purity for full characterization purposes. Nonetheless, this was a promising result that kept us invested in this synthetic route.

## 3-5: Elaboration of the Western Hemisphere

### 3-5-1: Attempted Tamao-Kumada Oxidation of (+)-3.4

Having found successful conditions for the conjugate reduction of (+)-**3.28**, we turned our attention towards elaboration of the western hemisphere. We chose to explore the Tamao-Kumada oxidation of the siloxane in the less advanced intermediate (+)-**3.4**; given

it was an easily handled solid, and did not contain incompatible functional groups. Unfortunately, we quickly discovered that the siloxane ring was completely inert to the oxidation (Scheme 3.19). Typical oxidation conditions (various sources of fluoride, bicarbonate salts, and $H_2O_2$ in various solvents)[14] led to recovery of starting material, even at high temperatures. On the other hand, strongly basic conditions ($CsOH•H_2O$ or KH, *t*-BuOOH)[15] resulted in decomposition.



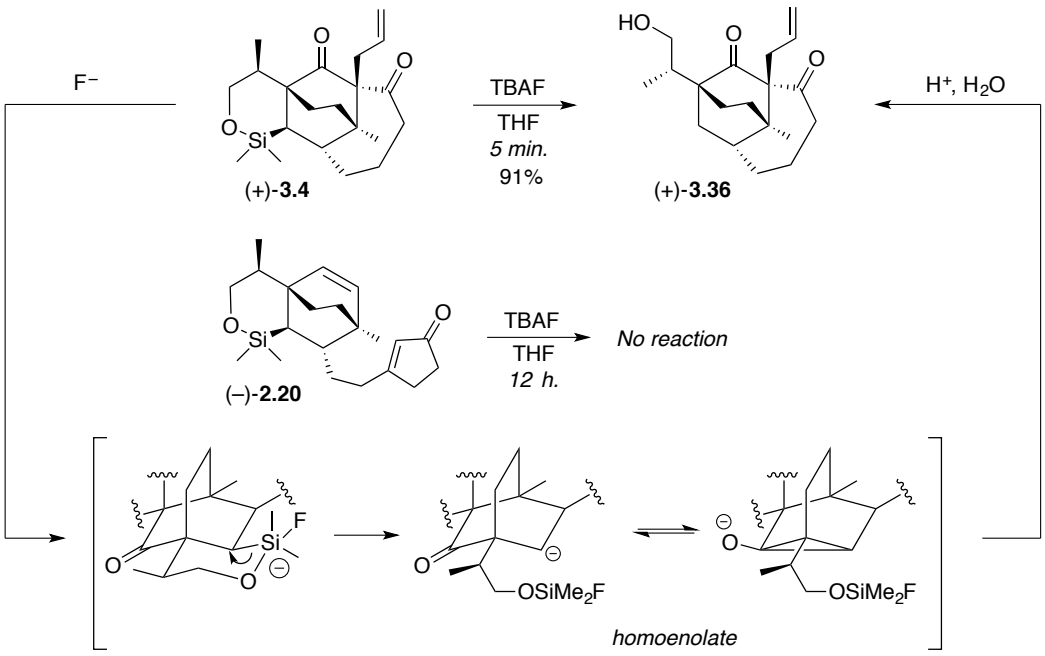

(+)-**3.4** **3.35**

| Entry | Conditions | Result |
|---|---|---|
| 1 | KF, $KHCO_3$, $H_2O_2$<br>THF/MeOH (1:1), rt → reflux | No reaction |
| 2 | CsF, $CsOH•H_2O$, *t*-BuOOH<br>NMP, rt → 70 °C | Decomposed |
| 3 | CsF, $KHCO_3$, $H_2O_2$<br>THF/MeOH (1:1), 70 °C | No reaction |
| 4 | TBAT, $KHCO_3$, $H_2O_2$<br>THF, 70 °C | No reaction |
| 5 | KH, *t*-BuOOH<br>DMF, rt → 70 °C | Decomposed |

**Scheme 3.19:** Unsuccessful Tamao-Kumada oxidation of (+)-**3.4**

An interesting case arose upon the use of TBAF and $H_2O_2$ in the presence of $KHCO_3$ that afforded a single new product in 91% yield, which was identified as (+)-**3.36**, resulting from desilylation rather than oxidation (Scheme 3.20). This outcome was quite unexpected since fluoride mediated desilylations of alkylsilanes typically require elevated temperatures, large excesses of fluoride, and extended reaction times. To gain insight into this process, two side by side experiments were conducted. In the first, (+)-**3.4** was

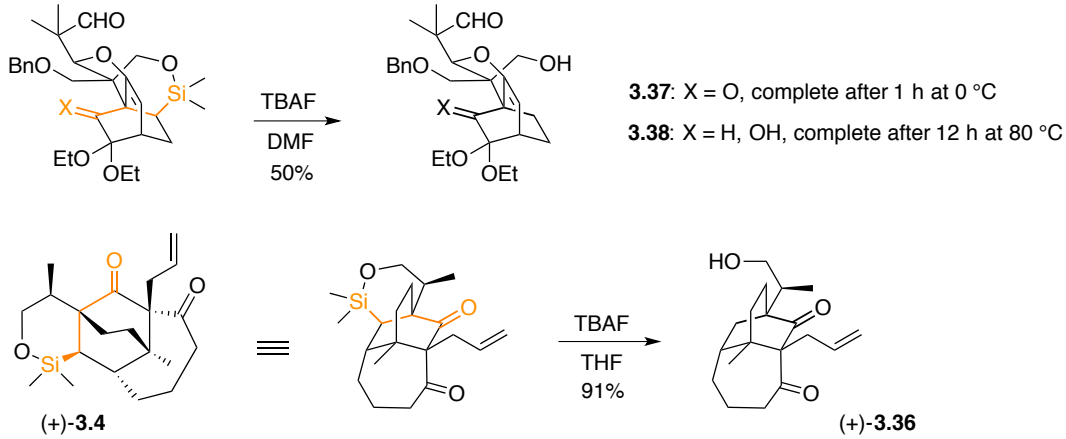
treated simply with TBAF in THF. In the second, an earlier substrate, (–)-**2.20**, lacking a carbonyl group at C(1) was subjected to the same conditions. While (+)-**3.4** was rapidly desilylated, no reaction occurred for (–)-**2.20**.




**Scheme 3.20:** Difference in Reactivity Between (+)-**3.4** and (–)-**2.20**; Hypothesis for the Formation of (+)-**3.36**

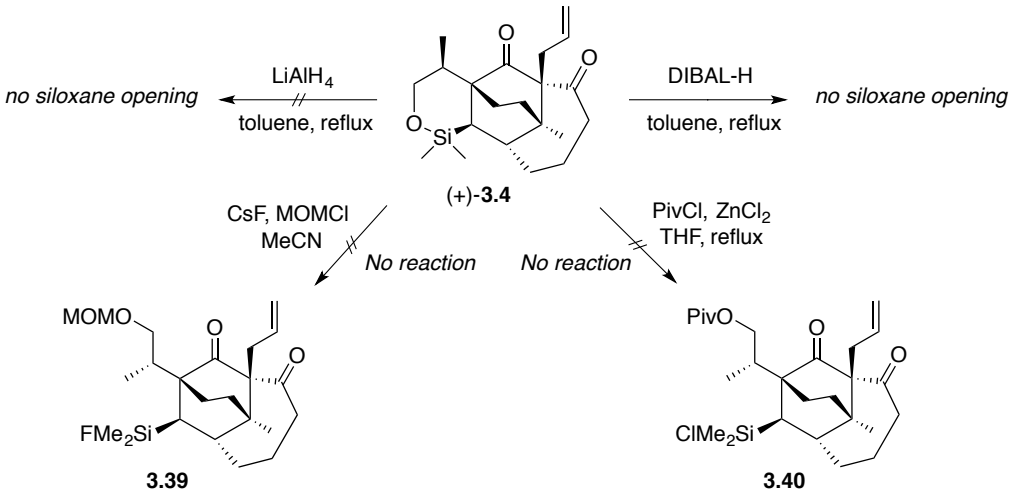
The reason for this difference in reactivity may be attributed to the electron stabilizing effect of the carbonyl group in (+)-**3.4**. Fluoride mediated desilylation of (+)-**3.4** would give a homoenolate type intermediate, which after an aqueous quench results in the undesired by-product (+)-**3.36**. Compound (–)-**2.20** does not bear a carbonyl group capable of stabilizing this anion, and therefore desilylation does not occur. Zakarian and coworkers noted a similar observation in a recent total synthesis of maoecrystal V (Scheme 3.21).[16] Ketone **3.37**, bearing a 1,3-relationship between the silyl group and the carbonyl in the bicyclo[2.2.2]octane system, was readily desilylated with TBAF at 0 °C

in 1 hour. The same substrate bearing a hydroxyl group (**3.38**) in place of the carbonyl required heating at 80 °C for 12 hours to bring about the desilylation.




**Scheme 3.21:** Comparison of the Desilylation of (+)-**3.4**, **3.37**, and **3.38**

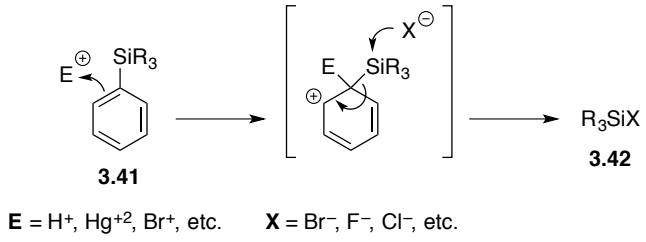
Besides cyclic silyl ethers, any silane bearing an alkoxy, ester, hydrogen, or halogen substituent can be oxidized to the corresponding alcohol. Thus, we attempted to transform the siloxane moiety of (+)-**3.4** into a more reactive silyl group, such as a silyl halide or silyl hydride (Scheme 3.22). Tamao reported a number of conditions for converting siloxanes into such activated silyl species with concomitant protection of the liberated hydroxyl group.[17] Unfortunately, subjection of (+)-**3.4** to all of the reported conditions led either to the recovery of starting material or decomposition. Surprisingly, even DIBAL-H or $LiAlH_4$ at high temperature (toluene, reflux) failed to open the siloxane.




**Scheme 3.22:** Attempted Activation of the Siloxane in (+)-**3.4**

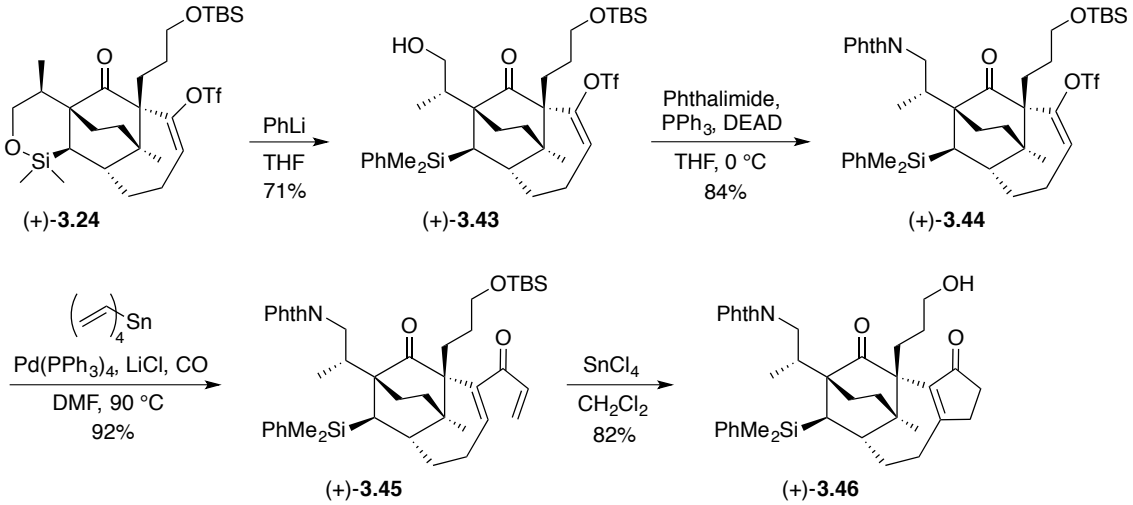
### 3-5-2: Synthesis of Diol (+)-3.48

Earlier studies had shown that the siloxane ring could be opened by treatment with phenyllithium to furnish the corresponding phenylsilane. Such phenylsilanes (**3.41**) can be converted to highly reactive silyl halides (**3.42**) employing protic acid or other electrophilic conditions (Hg salts, $Br_2$, $BF_3$•$OEt_2$, etc.; Scheme 3.23).[18] We reasoned that subjection of a phenylsilane derived from (+)-**3.4** to one of these conditions might afford an activated silane capable of undergoing the oxidation. This two step conversion of an arylsilane to a hydroxyl group was pioneered by Fleming, and is thus referred to as the Fleming-Tamao oxidation.[18]




**Scheme 3.23:** Conversion of Phenylsilanes to Activated Silyl Halides

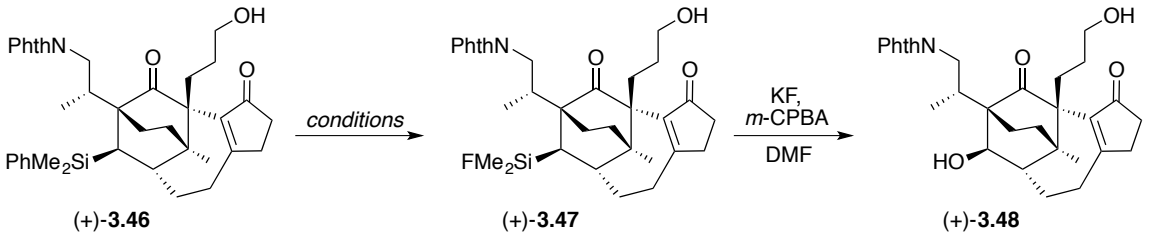
The phenyl group was readily introduced by exposure of (+)-**3.24** to phenyllithium, providing phenylsilane (+)-**3.43** in 71% yield (Scheme 3.24). Given that the strongly electrophilic conditions of protodesilylation are incompatible with unconjugated olefins, it was necessary to elaborate (+)-**3.43** further before investigating the oxidation of the phenylsilane. Rather than protect the primary hydroxyl of (+)-**3.43**, we opted to introduce the nitrogen at this point, which was accomplished by a Mitsunobu reaction with phthalimide to furnish (+)-**3.44** in 84% yield. We expected that the phthalimide should also serve as a stable protecting group for all of the endgame manipulations. Stille carbonylation of (+)-**3.44** under the previously established conditions (Scheme 3.12) then led to dienone (+)-**3.45** in 92% yield. The $SnCl_4$ promoted Nazarov cyclization was equally efficient in this system, providing the requisite substrate (+)-**3.46** for the Fleming-Tamao oxidation studies in 82% yield.




**Scheme 3.24:** Synthesis of Phenylsilane (+)-**3.46**

Fleming had reported a series of conditions for the one pot conversion of phenylsilanes (entries 1-3, Scheme 3.25) to the corresponding alcohols.[19] These conditions when applied to (+)-**3.46** led only to complex mixtures of products. Therefore,

we investigated just the electrophilic cleavage of the phenylsilane moiety. At the outset, the hindered phenylsilane was resistant to cleavage under typical conditions such as $BF_3$•$OEt_2$, $BF_3$•AcOH, and $Hg^{+2}$ salts. However, we found that exposure of (+)-**3.46** to $HBF_4$•$OEt_2$ in 1,2-dichloroethane at reflux converted the phenylsilane to the corresponding silyl fluoride (+)-**3.47**. We were delighted to find that treatment of (+)-**3.47** with KF and *m*-CPBA in DMF then resulted in successful Fleming-Tamao oxidation to deliver the advanced diol (+)-**3.48**. At this stage, the yield for the two steps could not be determined due the presence of inseparable impurities and/or by-products. As we will discuss, the lack of a yield at this point proved immaterial as a different reaction sequence that allowed us to move forward was discovered (*vide infra*).




(+)-**3.46** (+)-**3.47** (+)-**3.48**

| Entry | Conditions | Result |
|---|---|---|
| 1 | $Hg(OAc)_2$, AcOOH<br>THF, 25 °C → reflux | No reaction at 25 °C,<br>decomposed upon heating |
| 2 | $Hg(O_2CF_3)_2$, AcOOH<br>AcOH, TFA | Decomposed |
| 3 | KBr, NaOAc, AcOOH<br>THF, 25 °C | Complex mixture |
| 4 | $BF_3$•$OEt_2$<br>$CH_2Cl_2$, 25 °C | No reaction |
| 5 | $BF_3$•AcOH<br>$CH_2Cl_2$, 25 °C | No reaction |
| 6 | $HBF_4$•$OEt_2$<br>1,2-DCE, 80 °C | (+)-**3.47** confirmed by LCMS<br>and $^1$H NMR |

**Scheme 3.25:** Successful Fleming-Tamao Oxidation of Phenylsilane (+)-**3.46**

Having found a potential solution for introducing the C ring hydroxyl group and a strategy for the elaboration of the eastern hemisphere, we could now begin our final endgame studies.

## 3-6: References


1. Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135-1138.
2. Smith, A. B.; Levenberg, P. A. *Synthesis* **1981**, 567-570.
3. (a) Tsuji, J.; Takahash.H; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387-&. (b) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292-294.
4. Nazarov, I. N.; Zaretskaya, I. I.; Sorkina, T. I. *Zh. Obshch. Khim.* **1960**, *30*, 746-754.
5. Meyer, K. H.; Schuster, K. *Ber.* **1922**, *55B*, 819-823.
6. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636-3638.
7. Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320-&.
8. Merrifield, J. H.; Godschalx, J. P.; Stille, J. K. *Organometallics* **1984**, *3*, 1108-1112.
9. Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765-7770.
10. Weiss, M. E.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11501-11505.
11. Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616-&.
12. Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331-337.
13. Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314-7325.
14. (a) Tamao, K. *J. Syn. Org. Chem. Jpn.* **1988**, *46*, 861-878. (b) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694-1696.
15. Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044-6046.
16. Lu, P.; Gu, Z.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 14552-14555.
17. Tamao, K.; Yamauchi, T.; Ito, Y. *Chem. Lett.* **1987**, 171-174.

18. Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc. Chem. Commun.* **1984**, 29-31.

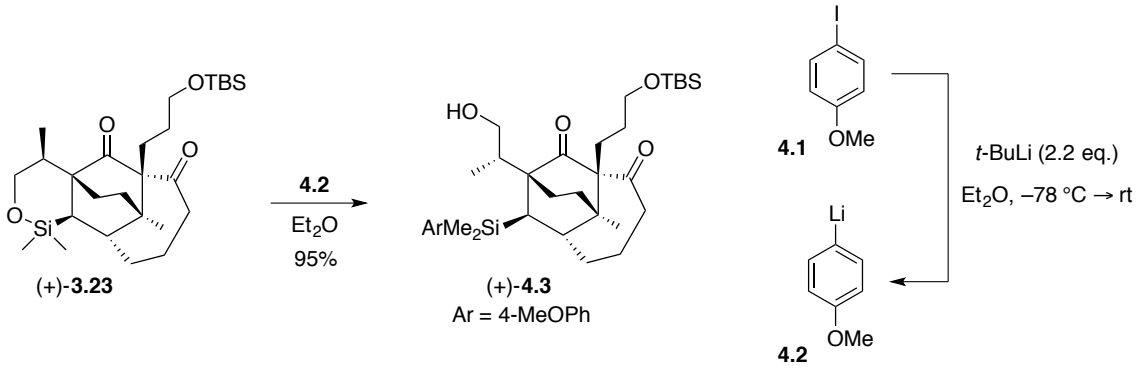
19. Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229-4232.

# CHAPTER 4

# Total Synthesis of (–)-Calyciphylline N

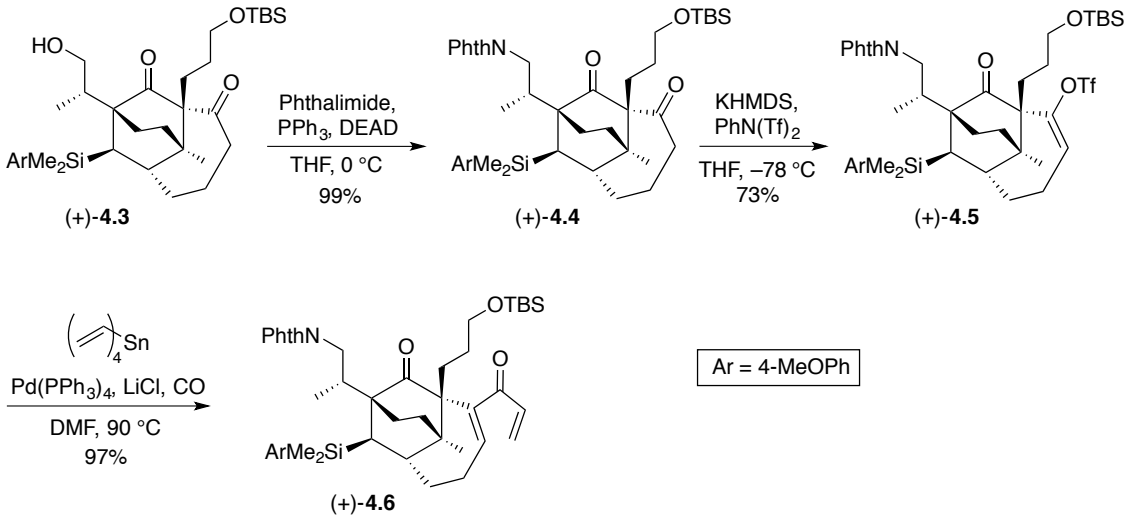
## 4-1: An Improved Route to Diol (+)-3.48

Despite having found a successful method for the Fleming-Tamao oxidation of (+)-**3.46**, the harsh conditions required to cleave the phenyl group ($HBF_4$•$OEt_2$, 1,2-DCE, 80 °C) resulted in the formation of inseparable by-products. We therefore developed an improved route towards diol (+)-**3.48**. Considering the mechanism of protodesilylation (Scheme 3.23), we anticipated that a more electron donating aryl substituent on the silicon, such as 4-methoxyphenyl, should significantly facilitate the protodesilylation step. Conceivably, introduction of the 4-methoxyphenyl group could be accomplished by siloxane opening with 4-methoxyphenyllithium (**4.2**), the latter prepared by lithiation of 4-iodoanisole (**4.1**) with *t*-BuLi. Treatment of (+)-**3.24** with **4.2** resulted in partial cleavage of the triflate; we therefore opted to introduce the aryl group at an earlier stage. To this end, exposure of (+)-**3.23** to **4.2** at room temperature cleanly afforded arylsilane (+)-**4.3** in excellent yield (Scheme 4.1). Notably, both of the hindered carbonyl groups remained completely inert to nucleophilic addition.



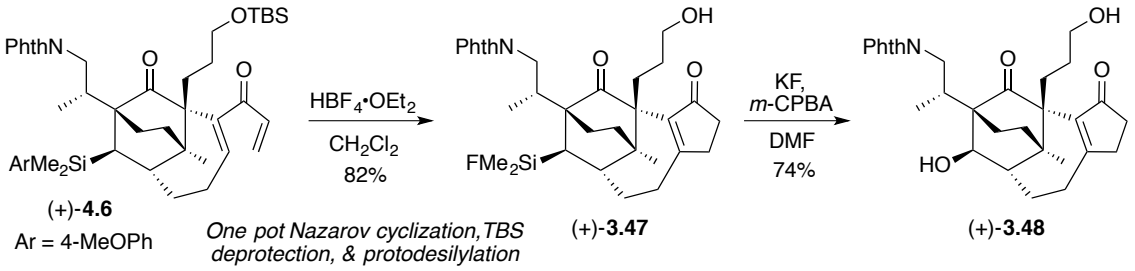

**Scheme 4.1:** Synthesis of Arylsilane (+)-**4.3**

Elaboration of (+)-**4.3** was achieved via the same sequence shown in Scheme 3.24. Thus, Mitsunobu reaction of (+)-**4.3** with phthalimide, followed by treatment of (+)-**4.4** with KHMDS and $PhN(Tf)_2$ delivered vinyl triflate (+)-**4.5** in 73% yield (Scheme 4.2). The Stille carbonylative coupling of (+)-**4.5** proceeded with high efficiency, affording divinyl ketone (+)-**4.6** in 97% yield.




**Scheme 4.2:** Synthesis of Divinyl Ketone (+)-**4.6**

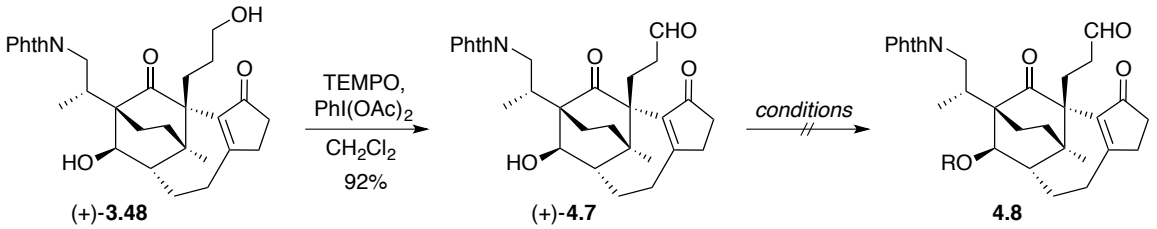
As described earlier, $HBF_4$•$OEt_2$ was found to be an effective reagent for the conversion of phenylsilane (+)-**3.46** to fluorosilane (+)-**3.47**. Given that Nazarov cyclizations can also be triggered with protic acid, we reasoned that both of these transformations could be achieved in a single flask. At the outset, of course, we could not anticipate the facility with which the 4-methoxyphenyl group could be cleaved. We were therefore delighted to find that treatment of (+)-**4.6** with $HBF_4$•$OEt_2$ in $CH_2Cl_2$ at ambient temperature cleanly afforded fluorosilane (+)-**3.47** in 82% yield. Pleasingly, Fleming-Tamao oxidation (KF, *m*-CPBA, DMF) of (+)-**3.47** then provided diol (+)-**3.48** in 74% yield.




**Scheme 4.3:** Improved Synthesis of Diol (+)-**3.48**

## 4-2: Synthesis of Diene Aldehyde (+)-4.12

Moving forward, in order to minimize the number of protecting group manipulations, we chose to oxidize intially the primary hydroxyl group. To this end, oxidation of (+)-**3.48** with TEMPO and $PhI(OAc)_2$[1] delivered aldehyde (+)-**4.7** in 92% yield (Scheme 4.4). Installation of a number of different protecting groups onto the secondary hydroxyl was explored next. However, protection of the hindered secondary hydroxyl in the presence of a relatively unhindered aldehyde was found to be difficult. Any conditions involving formation of an alkoxide (e.g., NaH, BnBr) led immediately to decomposition, again presumably through retro-aldol pathways. In several instances we did observe formation of the desired products, but these products were accompanied by significant amounts of decomposition or by-products.

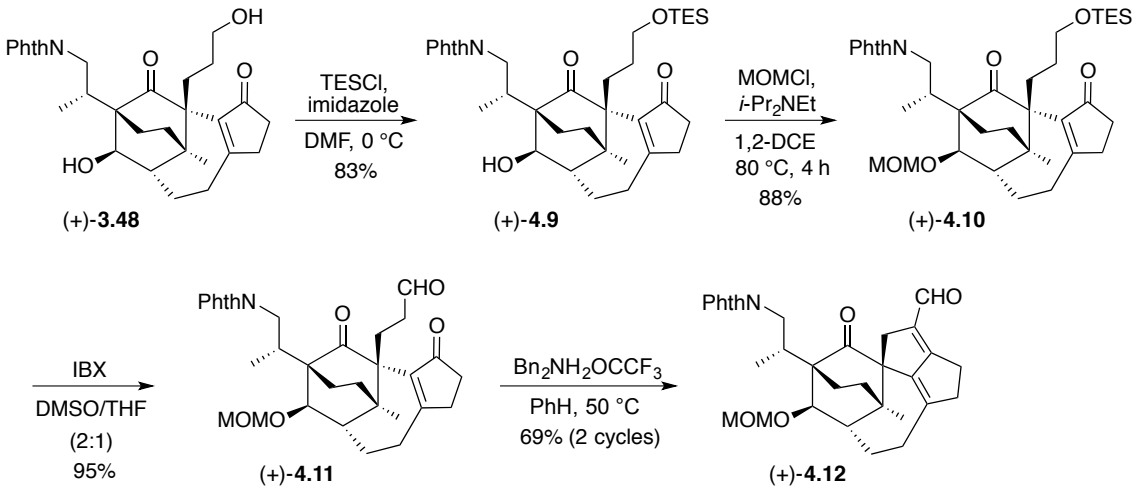



| Entry | Conditions | Result |
|---|---|---|
| 1 | BOMCl, TBAI, *i*-$Pr_2NEt$<br>$CH_2Cl_2$ | Significant decomposition |
| 2 | BzCl, pyridine<br>$CH_2Cl_2$ | Decomposed |
| 3 | $Bz_2O$, pyridine, DMAP<br>$CH_2Cl_2$ | Significant decomposition |
| 4 | NaH, BnBr<br>THF | Decomposed |

**Scheme 4.4:** Attempted Protection of the Secondary Alcohol of (+)-**4.7**

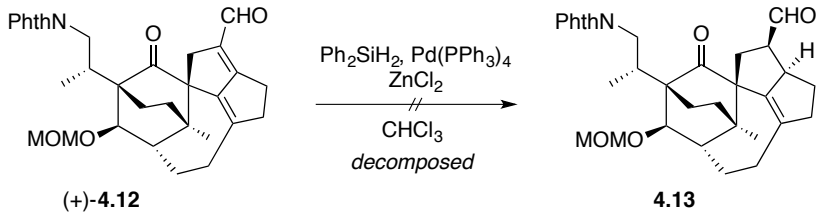
Given the difficulties associated with protection of the secondary hydroxyl in the presence of the aldehyde, we opted for a strategy involving differentiation of the hydroxyl groups prior to elaboration of the eastern hemisphere. Chemoselective protection of the primary hydroxyl was readily achieved by treatment of (+)-**3.48** with TESCl and imidazole in DMF (Scheme 4.5). Under these conditions, the secondary hydroxyl was completely unreactive. We anticipated that a MOM acetal would survive all the remaining manipulations of the endgame. Furthermore, the last step in the Carreira synthesis of (+)-daphmanidin E entailed deprotection of a similar MOM protected secondary hydroxyl, suggesting a similar outcome in our system as well. Installation of the MOM group onto the hindered secondary hydroxyl of (+)-**4.9** proved sluggish, with very low conversions observed even after 12 hours at room temperature and a large excess of MOMBr. Fortunately, heating (+)-**4.9** with MOMBr and *i*-$Pr_2NEt$ in 1,2-dichoroethane at 80 °C provided (+)-**4.10** in 4 hours and 88% yield. Upon treatment with

IBX, primary TES ethers can be converted to the corresponding alcohols, which are then oxidized to aldehydes under the reaction conditions.[2] Exposure of (+)-**4.10** to excess IBX in DMSO/THF led directly to the desired aldehyde (+)-**4.11** in 95% yield. Aldol condensation of (+)-**4.11** under the previously established conditions ($Bn_2NH_2O_2CCF_3$, PhH, 50 °C) then afforded diene aldehyde (+)-**4.12** in 69% yield after 2 cycles. While carrying out this particular reaction appears operationally simple, a great deal of optimization was required to maximize the yield of (+)-**4.12**. First, careful control of temperature was essential as heating the reaction to 60 °C caused an increased amount of decomposition. Best conditions involved running the reaction to ~70% conversion and recovering the starting material, as prolonged heating also resulted in decomposition. Finally, (+)-**4.12** appeared to be unstable to silica gel chromatography, as purification by this method led to low yields. Purification by preparative TLC was much more effective, providing consistently ≥60% yield of (+)-**4.12**.




**Scheme 4.5:** Synthesis of Diene Aldehyde (+)-**4.12**

With an effective means of preparing (+)-**4.12**, we next turned our attention to the critical 1,4-reduction (Scheme 4.6). Much to our disappointment, application of the successful reduction protocol identified for model substrate (+)-**3.28** (Scheme 3.18) resulted only in decomposition.



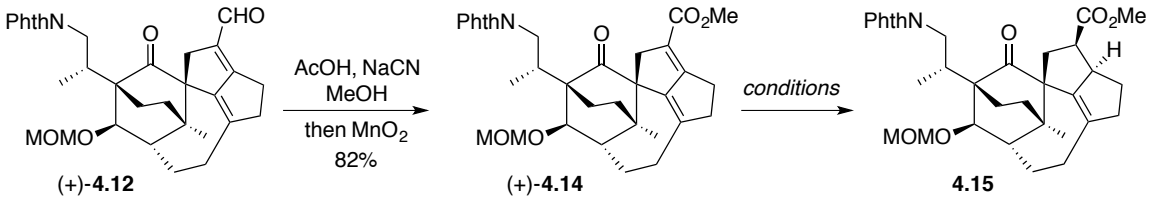

**Scheme 4.6:** Unsuccessful Conjugate Reduction of Diene Aldehyde (+)-**4.12**

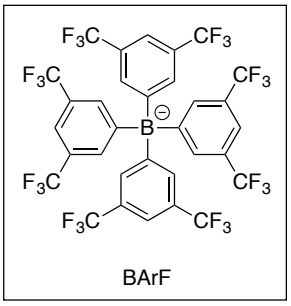
## 4-3: Completion of the Eastern Hemisphere

The dramatic change in reactivity from substrate (+)-**3.28** to (+)-**4.12** was both a frustrating and discouraging setback, considering the amount of experimentation that was necessary to identify these conditions. Undeterred, we decided to advance aldehyde (+)-**4.12** to the corresponding methyl ester (+)-**4.14** and investigate the homogeneous hydrogenation of this system. A reexamination of the literature revealed several reportedly highly active cationic hydrogenation catalysts that had not been explored with the model substrate (+)-**3.29**. As discussed earlier, we had demonstrated that hydrogenation of (+)-**3.29** with Crabtree's catalyst at 400 psi of $H_2$ resulted in reduction of one olefin with concomitant isomerization of the other.

Moving forward, oxidation of (+)-**4.12** (NaCN, AcOH, $MnO_2$, MeOH) furnished (+)-**4.14** in 82% yield; a series of hydrogenation catalysts were then screened (Scheme 4.7). In most cases, (+)-**4.14** was completely inert to reduction. Surprisingly, even hydrogenation with the Crabtree catalyst at 700 psi of $H_2$ also led to recovery of starting material.

In 2008, Pfaltz and coworkers reported that the reactivity of the Crabtree catalyst can be enhanced by replacing the $PF_6$ anion with that of tetrakis[bis(trifluoromethyl)-phenyl]borate (BArF).[3] The increase in reactivity is attributed to the extremely weakly coordinating nature of the BArF anion, facilitating coordination of functional groups to the cationic iridium center and resulting in increased catalytic activity. Hydrogenation of (+)-**4.14** with [(cod)(py)($PCy_3$)]IrBArF under 900 psi of $H_2$ afforded a mixture of diastereomers (4:1) in 84% yield.




| Entry | Conditions | Result |
|---|---|---|
| 1 | $PhMe_2SiH$, $Mo(CO)_6$<br>THF, reflux | No reaction |
| 2 | $H_2$ (1000 psi), [$(PPhMe_2)_3$(nbd)]$RhPF_6$<br>1,2-DCE, 25 °C, 16 h | No reaction |
| 3 | $H_2$ (700 psi), [(cod)(py)($PCy_3$)]$IrPF_6$<br>1,2-DCE, 25 °C, 16 h | No reaction |
| 4 | $H_2$ (1 atm), [(cod)(py)($PCy_3$)]IrBArF<br>1,2-DCE, 25 °C, 16 h | No reaction |
| 5 | $H_2$ (850 psi), [(cod)(py)($PCy_3$)]IrBArF<br>1,2-DCE, 25 °C, 16 h | 84%; 4:1 mixture of diastereomers |

**Scheme 4.7:** Hydrogenation of (+)-**4.14**

Analysis of the LCMS and $^{13}C$ NMR data indicated that a single double bond had been reduced. Moreover, the $^{1}H$ NMR immediately revealed significant differences in the region of interest when compared to the monounsaturated ester (+)-**3.31**. Consequently, a range of 2D NMR experiments were performed to establish the identity of the major product (Figure 4.1). In the HMBC spectrum, the hydrogens at C(13) and C(14) could

be assigned by virtue of their correlations to the ketone and ester functional groups, respectively. TOCSY NMR revealed uninterrupted coupling of the hydrogens from C(13) to C(17), indicating an isolated spin system. This analysis confirmed that the reduction was chemoselective for the α,β-double bond and, importantly, without isomerization of the remaining double bond. With the correct regiochemistry established, a NOESY experiment was performed to determine the configurations at the newly generated stereocenters, C(14) and C(15). An nOe correlation was observed between the C(21) methyl group and H(13α), which in turn showed a strong nOe to H(13β). Continuing with this analysis, H(13β) revealed a correlation to H(14), which displayed an nOe to H(15). Neither of the hydrogens [H(14) and H(15)] displayed an nOe correlation to the C(21) methyl group, indicating that these protons must be β. On the basis of this analysis, the structure of the major product could be confidently assigned as the desired diastereomer.

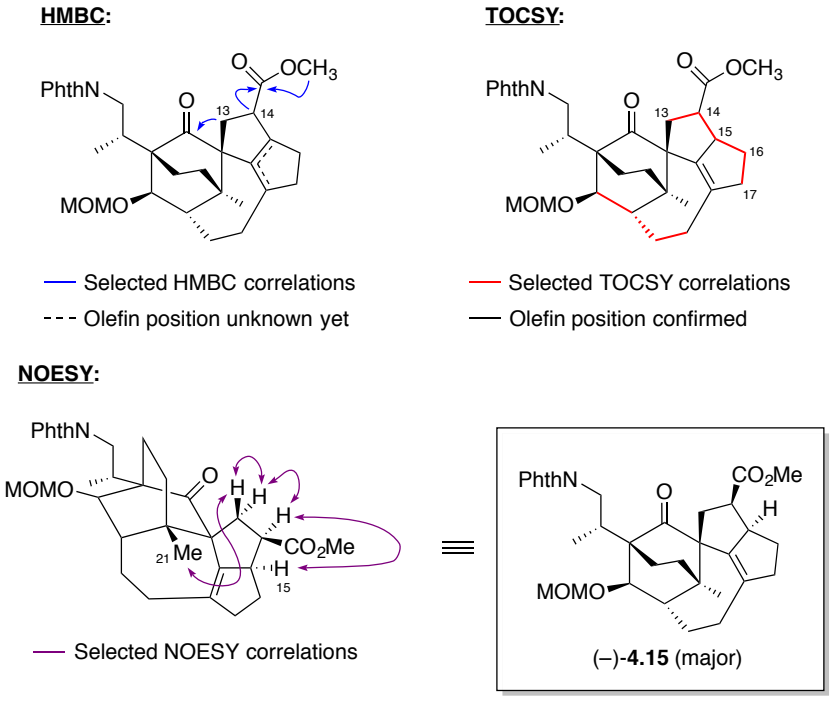
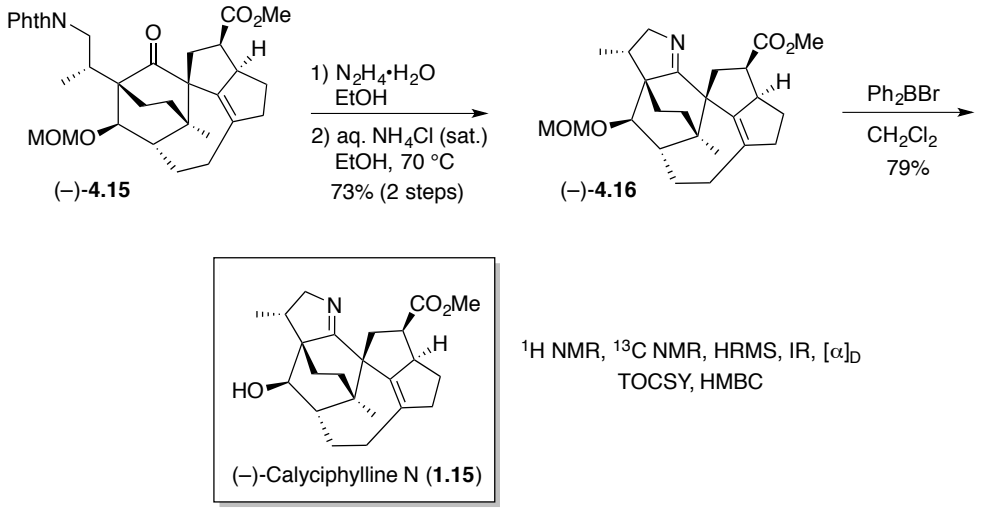



**Figure 4.1:** 2D NMR Analysis of (–)-**4.15**

## 4-4: Completion of the Total Synthesis of (–)-Calyciphylline N

With the eastern hemisphere constructed, all that remained to complete the synthesis of (–)-calyciphylline N were two deprotection steps and formation of the dihydropyrrole ring. Towards this end, removal of the phthalimide was cleanly achieved by treatment of (–)-**4.15** with $N_2H_4$•$H_2O$ in EtOH at room temperature (Scheme 4.8). The condensation was brought about by heating the resulting amine with aq. $NH_4Cl$ (sat.) in EtOH at 70 °C overnight, providing imine (–)-**4.16** in 73% yield (2 steps). Finally, Lewis acid $(Ph_2BBr)$[4] mediated removal of the MOM group delivered (–)-calyciphylline N (79%). Totally synthetic (–)-calyciphylline N displayed spectral properties in excellent agreement with those derived from the natural material [i.e., $^1H$ and $^{13}C$ NMR (500 and 125 MHz, respectively), HRMS parent ion identification, and chiroptic properties].




**Scheme 4.8:** Completion of the Synthesis

In summary, the first total synthesis of a calyciphylline alkaloid, (–)-calyciphylline N, has been achieved with a longest linear sequence of 40 steps from commercially available materials, quite comparable to the Carreira synthesis of (+)-daphmanidin E in 38 steps (longest linear sequence). Highlights of the synthesis include a substrate controlled,

intramolecular Diels-Alder reaction to form the bicyclic core and to set 4 contiguous stereocenters, a highly efficient Stille carbonylation/Nazarov cyclization sequence which permits construction of ring E, removes a protecting group, and activates the silyl moiety towards Fleming-Tamao oxidation, and an unprecedented, homogeneous hydrogenation of an exceptionally hindered diene ester to complete the eastern hemisphere.

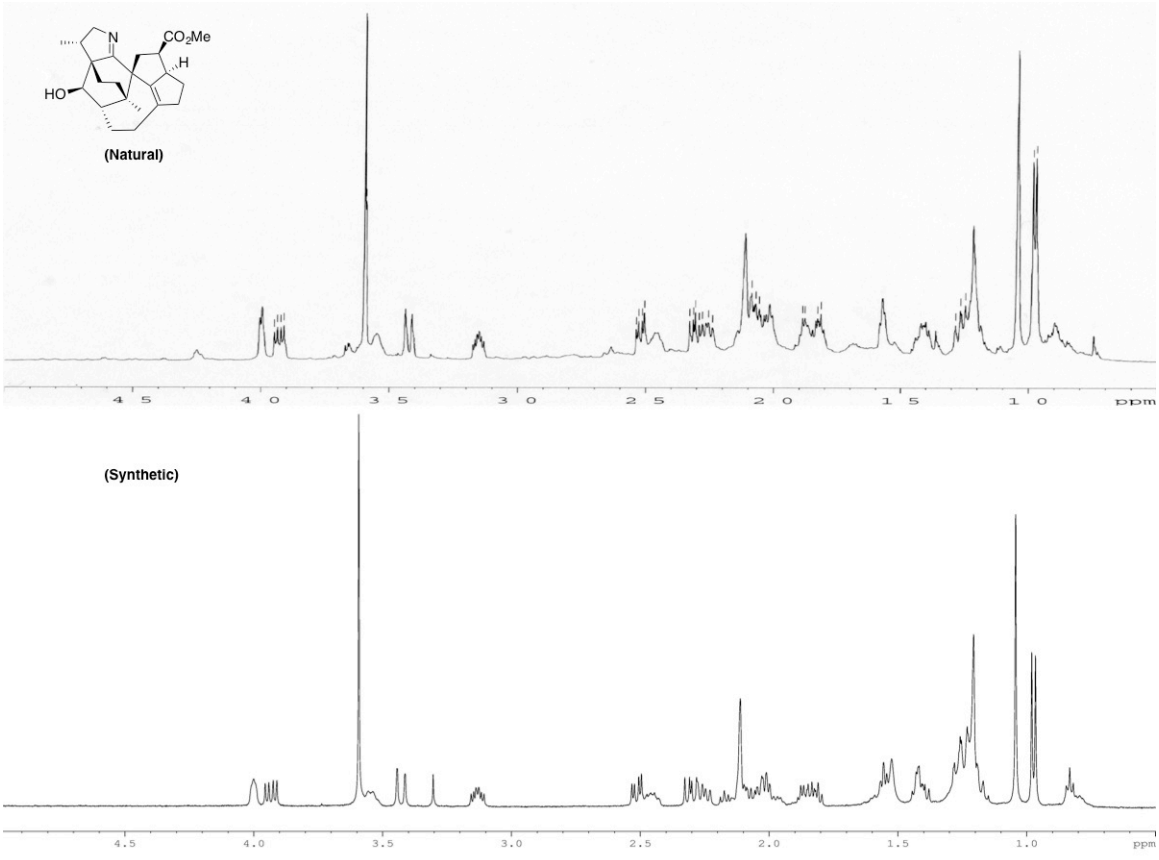



**Figure 4.2:** $^{1}$H NMR Spectra of (–)-Calyciphylline N (Natural vs. Synthetic)

| Chemical Shift (δ) Natural (–)-Calyciphylline N | Chemical Shift (δ) Synthetic (–)-Calyciphylline N | Δ δ (ppm) |
|---|---|---|
| 4.00 (d, *J* = 5.9 Hz, 1 H) | 4.00 (m, 1 H) | 0 |
| 3.93 (dd, *J* = 6.8, 15.6 Hz, 1 H) | 3.93, (dd, *J* = 7.0, 15.4 Hz, 1 H) | 0 |
| 3.66 (s, 3 H) | 3.59 (s, 3 H) | –0.07 |
| 3.54 (m, 1 H) | 3.56 - 3.52 (m, 1 H) | 0 |
| 3.42 (dd, *J* = 1.4, 15.6 Hz, 1 H) | 3.43 (dd, *J* = 1.2, 15.5 Hz, 1 H) | +0.01 |
| 3.13 (m, 1 H) | 3.13 (ddd, *J* = 5.3, 9.3, 10.7 Hz, 1 H) | 0 |
| 2.53 (dd, *J* = 5.0, 13.6 Hz, 1 H) | 2.51 (dd, *J* = 5.2, 13.5 Hz, 1 H) | –0.02 |
| 2.48 (m, 1 H) | 2.47 - 2.42 (m, 1 H) | 0.03 |
| 2.31 (dd, *J* = 9.4, 13.6 Hz, 1 H) | 2.30 (dd, *J* = 9.2, 13.6 Hz, 1 H) | –0.01 |
| 2.27 (dd, *J* = 8.6, 14.6 Hz, 1 H) | 2.25 (dd, *J* = 9.1, 15.5 Hz, 1 H) | –0.02 |
| 2.12 (m, 2 H)<br>2.12 (m, 1 H) | 2.19 - 2.09 (m, 3 H) | –0.02 |
| 2.06 (m, 1 H)<br>2.01 (m, 1 H) | 2.05 - 2.00 (m, 2 H) | - |
| 1.88 (m, 1 H) | 1.89 - 1.85 (m, 1 H) | +0.01 |
| 1.81 (m, 1 H) | 1.82 (dt, *J* = 7.3, 12.1 Hz, 1 H) | +0.01 |
| 1.56 (m, 1 H) | 1.57 - 1.54 (m, 1 H) | 0 |
| 1.41 (m, 1 H) | 1.42 - 1.38 (m, 1 H) | +0.01 |
| 1.27 (m, 1 H) | 1.26 (ddd, *J* = 2.2, 11.1, 13.3 Hz, 1 H) | –0.01 |
| 1.20 (m, 1 H) | 1.21 (m, 1 H) | +0.01 |
| 1.16 (m, 1 H) | 1.19 - 1.15 (m, 1 H) | +0.01 |
| 1.04 (s, 3 H) | 1.04 (s, 3 H) | 0 |
| 0.97 (d, *J* = 6.9 Hz, 3 H) | 0.97 (d, *J* = 7.1 Hz, 3 H) | 0 |

**Table 4.1:** $^{1}$H NMR Shifts of (–)-Calyciphylline N (Natural vs. Synthetic)

| Chemical Shift (δ) Natural (–)-Calyciphylline N | Chemical Shift (δ) Synthetic (–)-Calyciphylline N | Δ δ (ppm) |
|---|---|---|
| 185.7 | 185.3 | –0.4 |
| 176.2 | 176.2 | 0 |
| 141.2 | 141.4 | +0.2 |
| 132.2 | 132.1 | –0.1 |
| 67.6<br>67.8 | 68.0 | +0.2-0.4 |
| 57.0 | 57.0 | 0 |
| 54.3 | 54.4 | +0.1 |
| 52.6 | 52.6 | 0 |
| 51.8 | 51.9 | +0.1 |
| 51.0 | 51.1 | +0.1 |

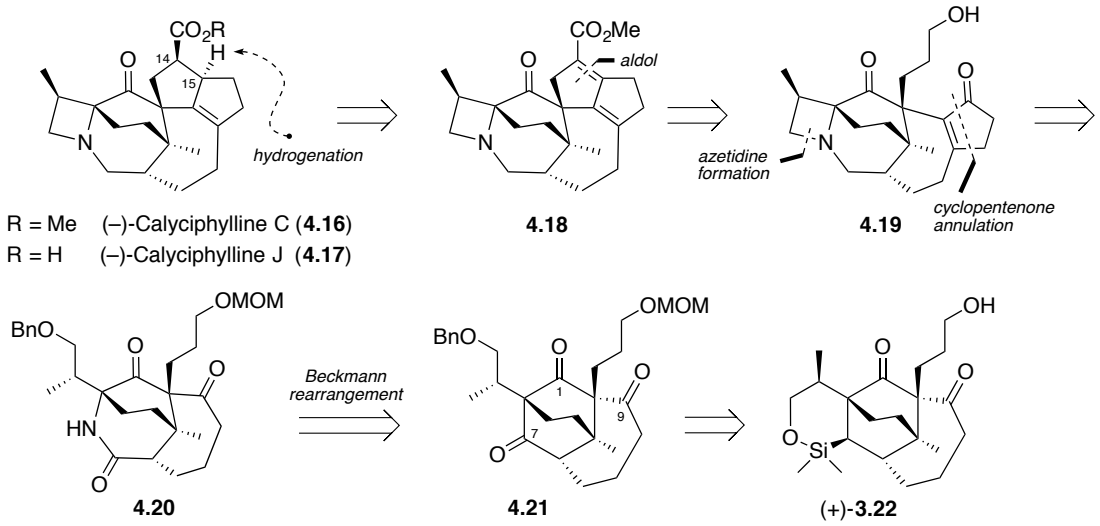
| | | |
|---|---|---|
| 42.7 | 42.7 | 0 |
| 42.2 | 42.3 | +0.1 |
| 39.4 | 39.5 | +0.1 |
| 38.8 | 38.8 | 0 |
| 37.0 | 37.0 | 0 |
| 34.6 | 34.6 | 0 |
| 27.3 | 27.4 | +0.1 |
| 25.2 | 25.3 | +0.1 |
| 23.3 | 23.4 | +0.1 |
| 22.8 | 22.7 | –0.1 |
| 21.4 | 21.5 | +0.1 |
| 16.6 | 16.7 | +0.1 |

**Table 4.2:** $^{13}$C NMR Shifts of (–)-Calyciphylline N (Natural vs. Synthetic)

## 4-4: Future Directions

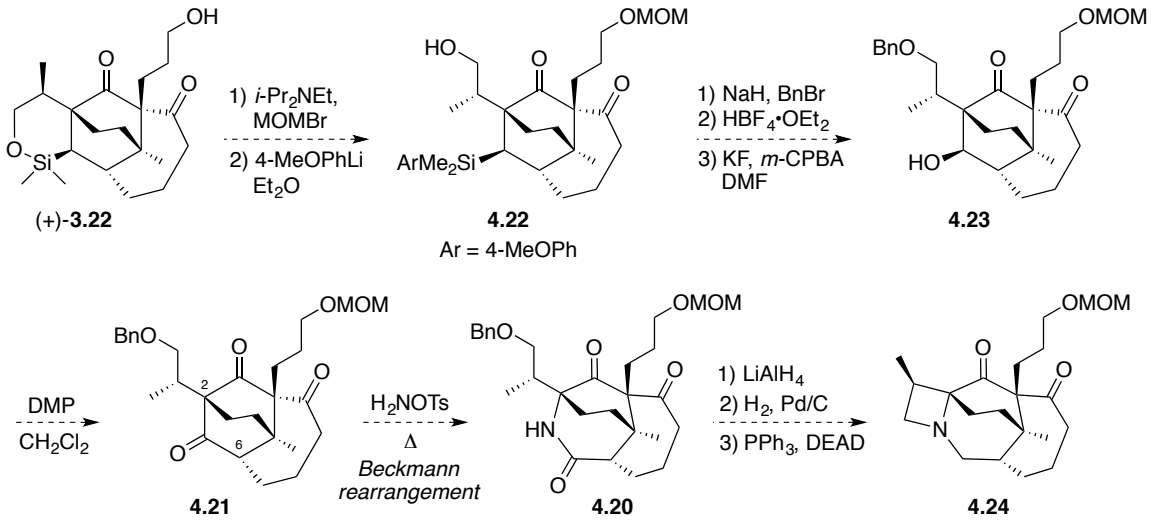
From the outset of this work, we also considered other members of the *Daphniphyllum* alkaloids that could be targeted based on our synthetic strategy. We became attracted by the possibility of accessing (–)-calyciphyllines C and J from the late stage intermediate, diketone (+)-**3.22**. Retrosynthetically (Scheme 4.9), a late stage hydrogenation of **4.18** that was successful in the (–)-calyciphylline N synthesis could be employed to set the stereochemistry at C(14) and C(15). An aldol condensation would assemble the diene ester, simplifying the structure to **4.19**. Again drawing inspiration from our work on (–)-calyciphylline N, a cyclopentenone annulation involving a Stille carbonylation/Nazarov cyclization sequence should permit access to ring E, while the azetidine ring could be constructed by a Mitsunobu cyclization, revealing lactam **4.20**. In turn, **4.20** could be assembled from **4.21** via a Beckmann rearrangement. We had shown in our work on the (–)-calyciphylline N synthesis that the C(1) and C(9) carbonyl groups were extremely resistant to nucleophilic addition. Therefore, chemoselectivity at the C(7) carbonyl group

is a distinct possibility in the Beckmann rearrangement step. Finally, **4.21** should be readily accessible through elaboration of diketone (+)-**3.22**.



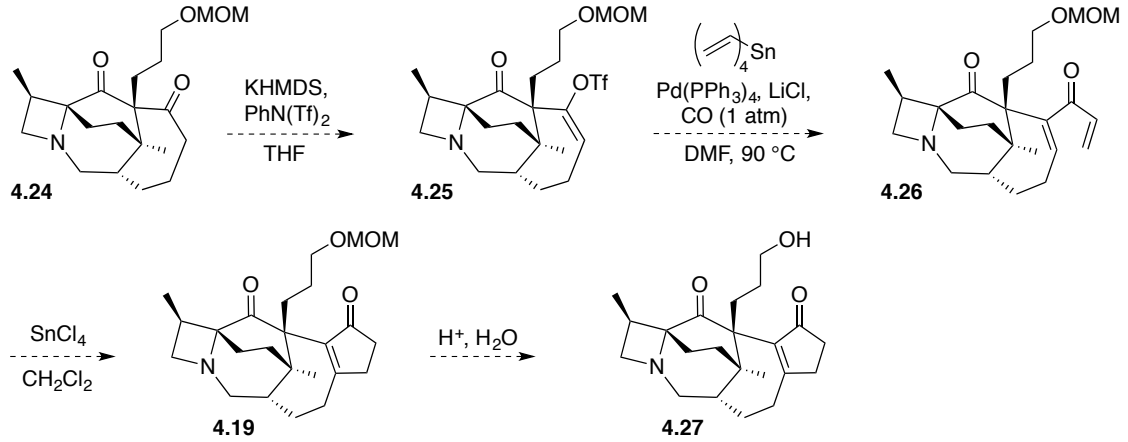

**Scheme 4.9:** Retrosynthetic Analysis of (–)-Calyciphyllines C and J

In the forward direction, protection of (+)-**3.22** as the MOM ether, followed by siloxane opening with 4-methoxyphenyllithium would provide alcohol **4.22** (Scheme 4.10). Benzyl protection of the primary alcohol and Fleming-Tamao oxidation of the arylsilane should next afford **4.23**. Oxidation of the resulting secondary hydroxyl would deliver the key intermediate **4.21**. Given that the migratory aptitude of the C(2) quaternary center should be greater than that of the C(6) tertiary center, a Beckmann rearrangement of **4.21** could be expected to provide **4.20** as the major regioisomer. Reduction of the lactam in **4.20** and removal of the benzyl protecting group would afford the corresponding amino alcohol. Formation of the azetidine ring could then be accomplished under Mitsunobu conditions to provide **4.24**.



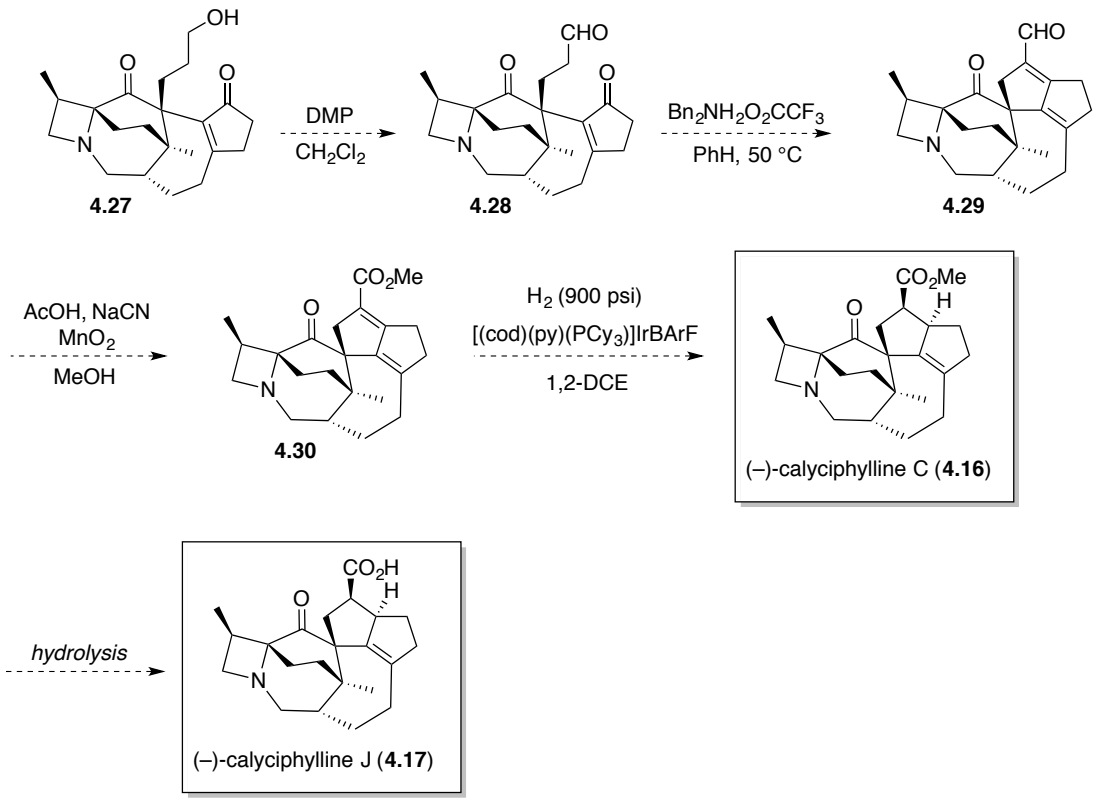

**Scheme 4.10:** Proposed Synthesis of Diketone **4.24**

Conversion of **4.24** to vinyl triflate **4.25** could be accomplished under previously established conditions (KHMDS, $PhN(Tf)_2$), and in turn our Stille carbonylation/Nazarov cyclization strategy [(–)-calyciphylline N, ring E synthesis) could next provide access to **4.19** (Scheme 4.11). Removal of the MOM acetal under protic or Lewis acidic conditions should then deliver **4.27**.




**Scheme 4.11:** Proposed Synthesis of Enone **4.27**

Oxidation of **4.27** to aldehyde **4.28**, followed by an aldol condensation should then lead to diene aldehyde **4.29**. In turn, **4.29** could then be oxidized to the corresponding methyl ester **4.30** (Scheme 4.12). Finally, hydrogenation of the diene ester would afford (–)-calyciphylline C, saponification of which would then lead to (–)-calyciphylline J.




**Scheme 4.12:** Proposed Endgame Towards the Total Synthesis of (–)-Calyciphyllines C and J

## 4-5: References

1. De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974-6977.

2. Wu, Y. K.; Huang, J. H.; Shen, X.; Hu, Q.; Tang, C. J.; Li, L. *Org. Lett.* **2002**, *4*, 2141-2144.

3. Wuestenberg, B.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, *350*, 174-178.

4. Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912-3920.

# CHAPTER 5

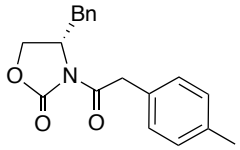
# Experimental Information

## 5-1: Materials and Methods

Reactions were conducted in oven- or flame-dried glassware under an atmosphere of nitrogen or argon, unless otherwise noted. All solvents were reagent grade. All chemicals were purchased from commercial vendors, unless otherwise referenced. Anhydrous tetrahydrofuran, diethyl ether, dichloromethane, and toluene were obtained from a Pure Solve$^{TM}$ PS-400 solvent purification system. Chloroform was purchased from Fischer Scientific (HPLC grade, contains approx. 0.75% ethanol as a preservative). Triethylamine, diisopropylamine, and diisopropyl ethylamine were freshly distilled from $CaH_2$. Reactions were magnetically stirred unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) with 250 mm Silicycle pre-coated silica gel plates or by LCMS [analytical reverse-phased (Sunfire C18; 4.6 mm Å~ 50 mm, 5 mL) high-performance liquid chromatography with a Waters binary gradient module 2525 equipped with Waters 2996 PDA and Waters micromass ZQ]. Silica gel flash chromatography was performed using ACS grade solvents and silica gel from Silicycle or Sorbent Technologies. Preparative TLC was performed using ACS grade solvents and 500 mm Silicycle pre-coated silica gel plates. Medium pressure liquid chromatography purification was performed using an apparatus comprised of a solvent pump (Waters 510 HPLC pump), injection loop (5 mL), column (20 mm ID x 300 mm, ACE glass) packed with silica gel (particle size 18-32 micron, 60 Å pore size), a refractive index detector (Waters Associates Differential Refractometer R401), and a chart recorder. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

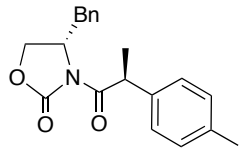
All melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Jasco Model FT/IR-480 Plus spectrometer. Proton and carbon NMR spectra were recorded on Bruker Avance III 500 MHz spectrometer equipped with either an Oxford cryomagnet or a Spectrospin/Bruker cryomagnet (500MHZ/52mm) with a 5 mm dual cryo probe. Chemical shifts are reported relative to chloroform (δ 7.26) for $^{1}$H-NMR and chloroform (δ 77.16) or benzene (δ 128.0) for $^{13}$C-NMR. Optical rotations were measured on a Jasco P-2000 polarimeter. High-resolution mass spectra (HRMS) were measured at the University of Pennsylvania on either a Waters LC-TOF mass spectrometer (model LCTXE Premier) or a Waters GCT Premier spectrometer. Single crystal X-ray structures were determined at the University of Pennsylvania. X-ray intensity data were collected on a Rigaku Mercury CCD or Bruker APEXII CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) at a temperature of 143(1) K.

## 5-2: Experimental Procedures Relevant to Chapter 2



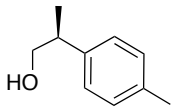

**Imide (+)-2.10:** A 2 L round bottom flask fitted with a mechanical stirrer and 50 mL addition funnel was charged with *p*-tolylacetic acid (12.0 g, 80.6 mmol) and THF (160 mL). The resulting solution was cooled to –78 °C and $Et_3N$ (11.6 mL, 84.0 mmol) was added dropwise via addition funnel. Pivaloyl chloride (9.8 mL, 80.6 mmol) was added dropwise via addition funnel and the resulting turbid white reaction mixture was stirred at –78 °C for 1 hour. In a separate flask, (*S*)-4-benzyl-2-oxazolidinone (11.9 g, 67.2 mmol) was dissolved in THF (140 mL) and cooled to –78 °C. A solution of *n*-BuLi (2.5M/hexanes, 32.3 mL, 80.6 mmol) was added dropwise via addition funnel and the resulting deep red solution was stirred at –78 °C for 40 minutes. The solution of lithiated oxazolidinone was transferred via cannula to the solution of the mixed anhydride over 1 hour at –78 °C. The reaction mixture was allowed to warm to room temperature and was quenched with saturated aqueous $NH_4Cl$ (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting white solid was triturated with pentane (100 mL x 3) to provide the title compound (17.9 g, 86%) as a crystalline white solid. $[\alpha]_D^{20}$ +64.0 (*c* 0.63 $CHCl_3$). **IR** (neat) 2918, 2857, 1779, 1697, 1389, 1358 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.33 - 7.25 (m, 3 H), 7.25 - 7.21 (m, 2 H), 7.19 - 7.11 (m, 4 H), 4.67 (tdd, *J* = 3.2, 7.3, 10.7 Hz, 1 H), 4.34 - 4.21 (m, 2 H), 4.21 - 4.14 (m, 2 H), 3.27 (dd, *J* = 3.2, 13.5 Hz, 1 H), 2.75 (dd, *J* = 9.5, 13.5 Hz, 1

H), 2.35 (s, 3 H). **$^{13}$C NMR** (125 MHz , $CDCl_3$) δ 171.6, 153.5, 137.0, 135.3, 130.6, 129.8, 129.6, 129.5, 129.1, 127.5, 66.3, 55.5, 41.3, 37.9, 21.3. **HRMS(ES+)** *m/z* 332.1255 [$(M+Na)^+$; calcd for $C_{19}H_{19}NO_3Na$: 332.1263].

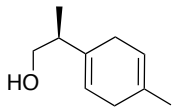



**Imide (+)-2.11:** To a solution of imide (+)-**2.10** (17.9 g, 57.9 mmol) in THF (250 mL) at –78 °C was added NaHMDS (1 M/THF, 64 mL, 63.7 mmol) dropwise via addition funnel. The resulting light orange solution was stirred at this temperature for 1 h. Methyl iodide (17.2 mL, 278 mmol) was added dropwise via addition funnel and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous $NH_4Cl$ (200 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (8:1 hexanes/EtOAc) to afford the title compound (14 g, 75%) as a highly viscous, greenish oil. $[\alpha]_D^{20}$ +141 (*c* 1.39 $CHCl_3$). **IR** (neat) 2975, 2919, 1779, 1697, 1379, 1360, 1234, 1210, 1189 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.39 - 7.33 (m, 2 H), 7.32 - 7.27 (m, 3 H), 7.27 - 7.22 (m, 2 H), 7.15 (app d, *J* = 7.9 Hz, 2 H), 5.12 (q, *J* = 7.0 Hz, 1 H), 4.60 (dddd, *J* = 2.4, 3.2, 7.6, 9.7 Hz, 1 H), 4.11 (dd, *J* = 2.4, 9.1 Hz, 1 H), 4.06 - 3.99 (m, 1 H), 3.36 (dd, *J* = 3.2, 13.3 Hz, 1 H), 2.83 (dd, *J* = 9.6, 13.4 Hz, 1 H), 2.34 (s, 3 H), 1.56 (d, *J* = 6.9 Hz, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 174.8, 152.9, 137.4, 136.9, 135.5, 129.5, 129.4, 129.0, 128.1, 127.4, 65.9, 55.8,

42.8, 38.0, 21.1, 19.5. **HRMS(ES+)** *m/z* 346.1409 [$(M+Na)^+$; calcd for $C_{20}H_{21}NO_3Na$: 346.1419].

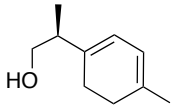



**Alcohol (–)-2.12:** To a solution of imide (+)-**2.11** in THF/$H_2O$ (1:1, 180 mL) was added $NaBH_4$ (6.55 g, 173.2 mmol) portion wise at 0 °C. The reaction mixture was warmed to room temperature and vigorously stirred overnight. The reaction mixture was diluted with EtOAc (100 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. After removal of the solvent, (*S*)-4-benzyl-2-oxazolidinone was recovered by filtration and washing with $Et_2O$ (200 mL). The washings, which contained the product, were concentrated *in vacuo* and the residue was distilled (78 °C/0.1 torr) to provide the title compound (5.94 g, 91%) as a colorless liquid. $[\alpha]_D^{20}$ –19.2 (*c* 0.82 $CHCl_3$). **IR** (neat) 3388, 2958, 2918, 2869, 2852, 1643 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.21 - 7.09 (m, 4 H), 3.68 (app d, *J* = 6.9 Hz, 2 H), 2.92 (sxt, *J* = 6.9 Hz, 1 H), 2.35 (s, 3 H), 1.27 (d, *J* = 7.1 Hz, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 140.7, 136.3, 129.4, 127.5, 68.8, 42.1, 21.1, 17.8. **HRMS(ES+)** *m/z* 150.1052 [$(M)^+$; calcd for $C_{10}H_{14}O$: 150.1045].



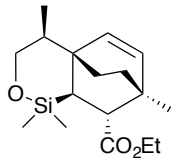

**Alcohol (–)-2.13:** Ammonia (1.2 L) was condensed at –78 °C into a 5-L round bottom flask fitted with a mechanical stirrer. A solution of alcohol (–)-**2.12** (28 g, 187 mmol) in absolute EtOH (190 mL) was added via cannula over 15 minutes. Lithium beads (6.47 g,

933 mmol) were added in portions until complete consumption of starting material ($^1$H NMR analysis). Excess lithium was quenched by further addition of EtOH (ca. 200 mL), followed by careful addition of saturated aqueous $NH_4Cl$, and the $NH_3$ was allowed to evaporate overnight under a stream of dry $N_2$. The residue was taken up in EtOAc (250 mL) and washed with water (100 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound (27.5 g, 99%) as a colorless liquid. $[\alpha]_D^{20}$ –2.0 (*c* 0.84 $CHCl_3$). **IR** (neat) 3355, 3019, 2961, 2923, 2875, 2819, 1640, 1039 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.55 (br. s., 1 H), 5.41 (br. s., 1 H), 3.53 - 3.43 (m, 2 H), 2.68 - 2.50 (m, 4 H), 2.32 (sxt, *J* = 6.9 Hz, 1 H), 1.66 (s, 3 H), 1.01 (d, *J* = 7.1 Hz, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 135.9, 131.4, 120.7, 118.5, 65.5, 43.2, 31.7, 27.2, 23.0, 15.5. **HRMS(ES+)** *m/z* 152.1206 [$(M)^+$; calcd for $C_{10}H_{16}O$: 152.1201].




**Alcohol 2.6:** DMSO (250 mL) was roughly degassed by bubbling $N_2$ through for 0.5 h. Solid KOtBu (83.6 g, 746 mmol) was added and the suspension was cooled to 0 °C. A solution of alcohol (–)-**2.13** (28.3 g, 187 mmol) in toluene (250 mL) was added dropwise via cannula over 20 minutes. The resulting solution was stirred at 0 °C for 1 h, then at room temperature for 2 h. After cooling back down to 0 °C, saturated aqueous $NH_4Cl$ (200 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (100 mL x 2), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was filtered through a short silica plug (4:1 hexanes/EtOAc) to afford an inseparable 3.5:1 mixture of **2.6** to **(–)-2.13** (27.5

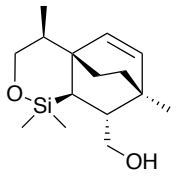
g, 97%). The following data is reported for this mixture. **IR** (neat) 3346, 2960, 2920, 2873, 2823, 1654, 1448, 1431, 1029 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) Diagnostic signals for **2.6**: δ 5.70 (d, *J* = 5.4 Hz, 1 H), 5.63 (d, *J* = 5.2 Hz, 1 H), 1.78 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) Major isomer **2.6**: δ 136.8, 134.7, 121.0, 119.3, 65.7, 43.2, 28.9, 24.4, 23.0, 15.3. **HRMS(ES+)** *m/z* 152.1205 [$(M)^+$; calcd for $C_{10}H_{16}O$: 152.1201].




**Ester (–)-2.4:** A solution of the silyl acrylate **2.7** (76.7 g, 328 mmol) in $CH_2Cl_2$ (820 mL) was cooled to 0 °C and TfOH (58 mL, 657 mmol) was added dropwise via addition funnel. After stirring for 1 h, the solution was cooled to –78 °C and pyridine (64 mL, 789 mmol) was added dropwise via addition funnel (pyridinium triflate precipitates). A solution of the alcohols **2.6** and **(–)-2.13** (40 g, 263 mmol) in $CH_2Cl_2$ (375 mL) was added dropwise via cannula over 0.5 h. After stirring for an additional 0.5 h, the reaction mixture was allowed to warm to room temperature and pentane (200 mL) was added. The reaction mixture was filtered through a short pad of celite, which was washed with additional pentane (100 mL), and the filtrate was concentrated *in vacuo*. The residue, which still contained some of the pyridinium salt, was redissolved in pentane (300 mL) and filtered once more. The filter cake was washed with pentane (100 mL) and the filtrate was concentrated *in vacuo* to provide triene **2.5** (93 g crude weight), which was used without purification.

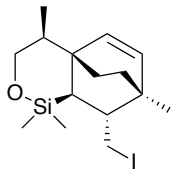
To a cooled (0 °C) solution of triene **2.5** in toluene (1.5 L) was added $Et_2AlCl$ (1 M/hexanes, 265 mL) dropwise over 1 h via addition funnel. The resulting solution was

stirred at 0 °C for 2 h, then allowed to stir at room temperature for 36 h. Upon completion, the reaction mixture was cooled to 0 °C and a saturated aqueous solution of Rochelle's salt (500 mL) was carefully added. The biphasic mixture was warmed to room temperature and vigorously stirred for 3 h. The layers were separated and the aqueous layer was extracted with EtOAc (300 mL) The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc) to afford the title compound (30 g, 50% over 2 steps, 9:1 d.r.; yield based on amount of **2.6**) as a light yellow liquid. $[\alpha]_D^{20}$ –50.2 (*c* 3.1 $CHCl_3$). **IR** (neat) 3037, 2955, 2908, 2873, 1736, 1637, 1462, 1371, 1250, 1158 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.28 (d, *J* = 8.3 Hz, 1 H), 5.94 (d, *J* = 8.3 Hz, 1 H), 4.09 (dq, *J* = 0.8, 7.1 Hz, 2 H), 3.74 - 3.66 (m, 2 H), 2.30 (d, *J* = 8.3 Hz, 1 H), 2.16 - 2.07 (m, 1 H), 1.71 - 1.64 (m, 1 H), 1.43 - 1.38 (m, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.23 - 1.20 (m, 2 H), 1.19 (s, 3 H), 0.89 (dd, *J* = 2.6, 8.3 Hz, 1 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 0.30 (s, 3 H), 0.09 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 175.4, 139.2, 134.8, 66.0, 60.2, 52.0, 41.2, 39.7, 37.7, 37.0, 35.6, 23.0, 21.4, 14.5, 12.6, 0.57, –2.63. **HRMS(ES+)** *m/z* 309.1896 [$(M+H)^+$; calcd for $C_{17}H_{29}O_3Si$: 309.1886].



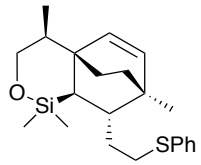

**Alcohol (–)-2.16:** Lithium aluminum hydride (4.8 g, 126 mmol) was suspended in $Et_2O$ (300 mL) and the suspension was cooled to 0 °C. In a separate flask, ester (–)-**2.4** (30 g, 97.4 mmol) was dissolved in $Et_2O$ (300 mL) and transferred to the $LiAlH_4$ suspension via cannula over 0.5 h. The reaction mixture was allowed to warm to room temperature and

was stirred for 1 h. Upon completion, the reaction mixture was cooled to 0 °C, and $H_2O$ (4.8 mL) was slowly added dropwise over 0.5 h. Next, an aqueous solution of NaOH (15%, 4.8 mL) was added, followed by additional $H_2O$ (14.4 mL). The suspension was warmed to room temperature and vigorously stirred for 15 minutes. The loose granular solid was filtered off and the filter cake was washed with $Et_2O$ (150 mL). The filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (4:1 hexanes/EtOAc) to afford the title compound (24.5 g, 94%) as a colorless oil. $[\alpha]_D^{20}$ –67.4 (*c* 0.4 $CHCl_3$). **IR** (neat) 3434, 3029, 2951, 2872, 1250, 1102, 1065 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.24 (d, *J* = 8.5 Hz, 1 H), 5.84 (d, *J* = 8.3 Hz, 1 H), 3.72 - 3.67 (m, 2 H), 3.42 (dd, *J* = 4.7, 10.8 Hz, 1 H), 3.33 (dd, *J* = 5.3, 10.8 Hz, 1 H), 2.08 – 2.01 (m, 1 H), 1.73 - 1.67 (m, 1 H), 1.57 (td, *J* = 5.0, 7.4 Hz, 1 H), 1.42 - 1.35 (m, 1 H), 1.20 (s, 3 H), 1.19 - 1.14 (m, 2 H), 0.82 (d, *J* = 7.1 Hz, 3 H), 0.45 (dd, *J* = 2.6, 7.5 Hz, 1 H), 0.25 (s, 3 H), 0.14 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 140.5, 135.0, 66.2, 66.1, 48.8, 41.3, 39.6, 36.8, 36.1, 36.0, 23.4, 22.1, 12.5, 1.16, –2.20. **HRMS(ES+)** *m/z* 267.1784 [$(M+H)^+$; calcd for $C_{15}H_{27}O_2Si$: 267.1780].



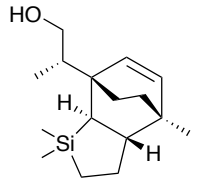

**Iodide (–)-2.17:** To a cooled (0 °C) solution of alcohol (–)-**2.16** (2.40 g, 9.02 mmol) in THF (36 mL) was added $PPh_3$ (2.48 g, 9.47 mmol), imidazole (1.22 g, 18.0 mmol), and $I_2$ (2.73 g, 10.8 mmol) sequentially. The cold bath was removed and the brown solution was stirred at room temperature for 10 min. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (15 mL) and the layers were separated. The aqueous layer was

extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (12:1 hexanes/EtOAc) to afford the title compound (2.87 g, 85%) as a colorless oil. $[\alpha]_D^{20}$ –32.1 (*c* 0.22 $CHCl_3$). **IR** (neat) 3034, 2953, 2916, 2869, 1636, 1462, 1370, 1250, 1104, 1070, 844 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.20 (d, *J* = 8.3 Hz, 1 H), 5.90 (d, *J* = 8.3 Hz, 1 H), 3.75 - 3.62 (m, 2 H), 3.16 (dd, *J* = 4.1, 10.2 Hz, 1 H), 2.95 (dd, *J* = 5.3, 10.2 Hz, 1 H), 2.07 (dddd, *J* = 5.0, 6.7, 11.7, 13.7 Hz, 1 H), 1.71 - 1.62 (m, 2 H), 1.41 - 1.33 (m, 1 H), 1.23 (s, 3 H), 1.18 - 1.13 (m, 2 H), 0.82 (d, *J* = 6.9 Hz, 3 H), 0.42 (dd, *J* = 2.1, 7.4 Hz, 1 H), 0.26 (s, 6 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 138.8, 134.2, 66.2, 47.8, 41.7, 40.0, 39.2, 38.8, 36.5, 22.9, 21.9, 13.7, 12.5, 2.4, –1.8. **HRMS(ES+)** *m/z* 377.0798 [$(M+H)^+$; calcd for $C_{15}H_{26}IOSi$: 377.0798].



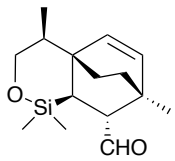

**Sulfide (–)-2.18:** To a solution of DABCO (10.7 mg, 96 μmol) and PhSMe (12 μL, 96 μmol) in THF (0.7 mL) was added *n*-BuLi (2.5M/hexanes, 38 μL, 96 μmol) dropwise at 0 °C. The resulting solution was stirred at 0 °C for 45 minutes and a solution of iodide (–)-**2.17** (20 mg, 53 μmol) in THF (0.3 mL) was added via cannula. The reaction mixture was allowed to warm to room temperature and stir for an additional 1 h. The reaction was quenched by the addition of saturated aqueous $NH_4Cl$ (2 mL), then diluted with $H_2O$ (5 mL) and $Et_2O$ (5 mL). The layers were separated and the aqueous layer was extracted with $Et_2O$ (5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography (30:1

hexanes/EtOAc) to afford the title compound (16 mg, 81%) as a colorless oil. $[\alpha]_D^{20}$ –25.8 (*c* 0.54 $CHCl_3$). **IR** (neat) 3029, 2951, 2915, 2856, 1650, 1583, 1438, 1249, 1103, 1070 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.30 - 7.25 (m, 4 H), 7.15 (ddd, *J* = 2.6, 5.7, 8.5 Hz, 1 H), 6.17 (d, *J* = 8.3 Hz, 1 H), 5.79 (d, *J* = 8.5 Hz, 1 H), 3.71 - 3.64 (m, 2 H), 2.78 (ddd, *J* = 2.6, 6.5, 9.4 Hz, 2 H), 2.01 (dt, *J* = 6.9, 14.1 Hz, 1 H), 1.72 - 1.67 (m, 1 H), 1.67 - 1.63 (m, 1 H), 1.52 (dt, *J* = 4.4, 6.7 Hz, 1 H), 1.39 - 1.29 (m, 2 H), 1.20 (dt, *J* = 3.8, 12.3 Hz, 1 H), 1.17 - 1.13 (m, 1 H), 1.12 (s, 3 H), 0.81 (d, *J* = 6.9 Hz, 3 H), 0.33 (dd, *J* = 2.8, 6.9 Hz, 1 H), 0.25 (s, 3 H), 0.09 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 139.0, 136.8, 135.1, 129.1, 129.0, 125.9, 66.2, 45.8, 41.3, 39.5, 38.6, 37.8, 35.6, 34.4, 31.7, 23.6, 22.2, 12.5, 1.6, –1.9. **HRMS(ES+)** *m/z* 372.1957 [$(M)^+$; calcd for $C_{22}H_{32}OSSi$: 372.1943].



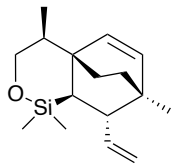

**Alcohol (–)-2.21:** To a solution of di-*tert*-butyl biphenyl (500 mg, 1.88 mmol) in THF (9.4 mL) was added a large excess of freshly scraped lithium beads. The reaction mixture was cooled to 0 °C and vigorously stirred. Within 15 minutes, the characteristic deep green color of LiDBB was observed. The reaction mixture was stirred at 0 °C for 4 hours to provide a 0.2 M solution of LiDBB. Sulfide (–)-**2.18** (20 mg, 53.7 μmol) was dissolved in THF (0.2 mL) and the solution of LiDBB was added until the green color persisted. The reaction was quenched with saturated aqueous $NH_4Cl$ (1 mL) and diluted with $Et_2O$ (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with $Et_2O$ (5 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The product was isolated by preparative TLC (4:1

hexanes/EtOAc) to afford the title compound (10 mg, 70%) as a colorless oil. $[\alpha]_D^{20}$ –85.7 (*c* 0.35 $CHCl_3$). **IR** (neat) 3314, 3029, 2935, 2898, 2865, 1636, 1249, 1023 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.36 (d, *J* = 8.3 Hz, 1 H), 5.77 (d, *J* = 8.3 Hz, 1 H), 3.88 (dd, *J* = 3.6, 10.5 Hz, 1 H), 3.42 (dd, *J* = 9.0, 10.2 Hz, 1 H), 1.78 - 1.67 (m, 2 H), 1.44 (dt, *J* = 4.0, 12.9 Hz, 1 H), 1.40 - 1.31 (m, 2 H), 1.25 (br s, 1 H), 1.17 - 1.10 (m, 2 H), 1.07 (s, 3 H), 1.04 (d, *J* = 6.7 Hz, 3 H), 0.71 (ddd, *J* = 1.4, 9.3, 15.1 Hz, 1 H), 0.67 - 0.58 (m, 1 H), 0.58 - 0.52 (m, 1 H), 0.20 (s, 3 H), 0.16 (s, 3 H), -0.11 (d, *J* = 13.3 Hz, 1 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 140.8, 135.6, 66.1, 52.4, 47.1, 43.2, 43.0, 41.6, 37.4, 26.4, 25.7, 22.0, 13.3, 12.3, –0.3, –1.8. **HRMS(ES+)** *m/z* 265.1977 [$(M+H)^+$; calcd for $C_{16}H_{29}OSi$: 265.1988].



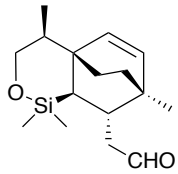

**Aldehyde (–)-2.22:** To a solution of alcohol (–)-**2.16** (100 mg, 0.38 mmol) in $CH_2Cl_2$ (2.5 mL) was added Dess-Martin periodinane (191 mg, 0.45 mmol) at room temperature. The turbid reaction mixture was stirred for 0.5 hours and quenched with saturated aqueous $Na_2S_2O_3$ (1 mL) and saturated aqueous $NaHCO_3$ (1 mL). The reaction mixture was vigorously stirred until the layers became clear (20 minutes). Additional water (4 mL) was added and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (5 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (12:1 hexanes/EtOAc) to afford the title compound (90.2 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$ –94.6 (*c* 0.41 $CHCl_3$). **IR** (neat) 3035, 2954, 2921, 2871, 2821, 2711, 1719, 1637,

1252, 1064 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 9.07 (d, *J* = 5.2 Hz, 1 H), 6.34 (d, *J* = 8.3 Hz, 1 H), 5.93 (d, *J* = 8.3 Hz, 1 H), 3.77 - 3.67 (m, 2 H), 2.18 - 2.08 (m, 2 H), 1.74 (dt, *J* = 3.6, 10.5 Hz, 1 H), 1.45 - 1.39 (m, 1 H), 1.28 - 1.19 (m, 2 H), 1.21 (s, 3 H), 0.86 (d, *J* = 7.1 Hz, 3 H), 0.79 (dd, *J* = 2.8, 7.1 Hz, 1 H), 0.28 (s, 3 H), 0.03 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 203.7, 141.1, 133.7, 66.0, 59.7, 40.8, 39.8, 36.6, 35.0, 31.8, 23.4, 21.7, 12.6, –0.1, –2.6. **HRMS(ES+)** *m/z* 264.1540 [$(M)^+$; calcd for $C_{15}H_{24}O_2Si$: 264.1546].




**Olefin (–)-2.23:** Methyl triphenylphosphonium bromide (81 mg, 0.23 mmol) was suspended in THF (1 mL) and cooled to 0 °C. A solution of NaHMDS (1 M/THF, 0.22 mL, 0.23 mmol) was added dropwise, and the resulting light orange solution was stirred at room temperature for 1 hour. The solution of the phosphorous ylide was cooled to 0 °C and a solution of aldehyde (–)-**2.22** (50 mg, 0.19 mmol) in THF (0.3 mL) was added by syringe. The reaction mixture was warmed to room temperature and quenched with saturated aqueous $NH_4Cl$ (1 mL). The reaction mixture was diluted with EtOAc (5 mL) and $H_2O$ (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (30:1 hexanes/EtOAc) to afford the title compound (39.6 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ – 70.7 (*c* 0.42 $CHCl_3$). **IR** (neat) 3073, 3033, 2953, 2923, 2868, 2854, 1638, 1251, 1096, 1066 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.24 (d, *J* = 8.3 Hz, 1 H), 5.81 (d, *J* = 8.5 Hz, 1

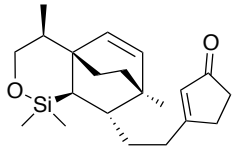
H), 5.23 (td, *J* = 9.9, 16.8 Hz, 1 H), 4.83 (dd, *J* = 2.0, 8.7 Hz, 1 H), 4.80 (s, 1 H), 3.75 - 3.63 (m, 2 H), 2.09 - 1.99 (m, 1 H), 1.92 (dd, *J* = 7.9, 9.3 Hz, 1 H), 1.70 (dt, *J* = 3.8, 13.3 Hz, 1 H), 1.35 (dt, *J* = 4.2, 12.1 Hz, 1 H), 1.29 - 1.25 (m, 1 H), 1.20 - 1.13 (m, 1 H), 1.05 (s, 3 H), 0.83 (d, *J* = 7.1 Hz, 3 H), 0.41 (dd, *J* = 2.8, 6.9 Hz, 1 H), 0.28 (s, 3 H), 0.06 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 143.7, 139.9, 134.6, 113.2, 66.1, 52.7, 41.0, 39.8, 38.9, 37.1, 35.3, 23.7, 21.9, 12.5, 1.0, –2.2. **HRMS(ES+)** *m/z* 262.1758 [$(M)^+$; calcd for $C_{16}H_{26}O_2Si$: 262.1753].




**Aldehyde (–)-2.28:** To a solution of iodide (–)-**2.17** (2.87 g, 7.63 mmol) in DMSO (17 mL) was added NaCN (561 mg, 11.4 mmol) and the reaction mixture was heated to 60 °C for 3 h. After cooling to room temperature, the solution was diluted with $Et_2O$ and water (20 mL each). The layers were separated and the aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was filtered through a silica plug (9:1 hexanes/EtOAc) and the product was used without further purification.

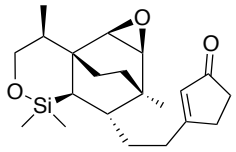
The resulting nitrile (1.99 g, 7.23 mmol) was dissolved in $CH_2Cl_2$ (25 mL), cooled to –78 °C, and DIBAL-H (1.5 M/toluene, 10.6 mL, 15.9 mmol) was added dropwise over 15 min. Excess DIBAL-H was quenched by the slow addition of EtOAc (5 mL) at –78 °C and the solution was allowed to warm to room temperature. Saturated aqueous Rochelle's salt (20 mL) was added and vigorous stirring was continued for 1.5 h. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (20 mL x 2). The combined

organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (13:1 hexanes/EtOAc) to afford the title compound (1.89 g, 91% over 2 steps) as a colorless oil. $[\alpha]_D^{20}$ –42.5 (*c* 0.78 $CHCl_3$). **IR** (neat) 3029, 2953, 2911, 2873, 2723, 1724, 1463, 1371, 1251, 1102, 1069, 834 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 9.71 (t, *J* = 2.4 Hz, 1 H), 6.23 (d, *J* = 8.5 Hz, 1 H), 5.77 (d, *J* = 8.3 Hz, 1 H), 3.68 (app d, *J* = 8.1 Hz, 2 H), 2.41 - 2.34 (m, 1 H), 2.05 - 1.92 (m, 3 H), 1.71 (ddd, *J* = 3.6, 9.9, 12.9 Hz, 1 H), 1.42 (ddd, *J* = 4.7, 10.1, 12.2 Hz, 1 H), 1.26 (dt, *J* = 3.8, 12.2 Hz, 1 H), 1.20 - 1.12 (m, 1 H), 1.10 (s, 3 H), 0.82 (d, *J* = 6.9 Hz, 3 H), 0.34 (dd, *J* = 2.9, 6.8 Hz, 1 H), 0.30 (s, 3 H), 0.11 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 202.9, 140.3, 134.2, 66.2, 50.6, 41.4, 41.2, 39.8, 39.5, 37.6, 35.3, 23.8, 22.0, 12.4, 1.49, –2.14. **HRMS(ES+)** *m/z* 279.1774 [$(M+H)^+$; calcd for $C_{16}H_{27}O_2Si$: 279.1780].



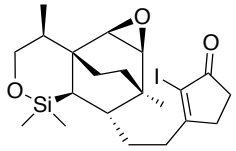

**Enone (–)-2.20:** Triphenylphosphine (1.59 g, 6.08 mmol) was dissolved in THF (20 mL) and TBSOTf (1.4 mL, 6.08 mmol) was added, followed by dropwise addition of 2-cyclopenten-1-one (0.5 mL, 6.08 mmol) at room temperature. After 45 min, TLC indicated complete consumption of the enone, and the solution was cooled to –78 °C. A solution of *n*-BuLi (2.37M/hexanes, 2.56 mL, 6.08 mmol) was added dropwise and the reaction mixture turned black. After stirring for an additional 0.5 h, a solution of the aldehyde (–)-**2.28** (846 mg, 3.04 mmol) in THF (4 mL) was added by syringe. The resulting solution was allowed to warm to room temperature and quenched with 1 M HCl

(10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (4:1 hexanes/EtOAc) to afford the title compound (954 mg, 91%) as a white solid. Crystals suitable for X-ray analysis were obtained by slow evaporation from ethyl acetate. Melting point 77-79 °C. $[\alpha]_D^{20}$ –26.5 (*c* 0.8 $CHCl_3$). **IR** (neat) 3028, 2951, 2870, 1709, 1616, 1250, 1103 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.19 (d, *J* = 8.3 Hz, 1 H), 5.91 - 5.86 (m, 1 H), 5.81 (d, *J* = 8.3 Hz, 1 H), 3.69 (app d, *J* = 7.9 Hz, 2 H), 2.54 (dd, *J* = 3.0, 4.8 Hz, 2 H), 2.41 - 2.34 (m, 2 H), 2.22 (dtd, *J* = 5.4, 16.1, 23.2 Hz, 2 H), 2.03 (qt, *J* = 7.3, 14.1 Hz, 1 H), 1.70 (ddd, *J* = 3.2, 9.9, 12.5 Hz, 1 H), 1.64 - 1.54 (m, 2 H), 1.46 (dt, *J* = 4.1, 6.9 Hz, 1 H), 1.40 - 1.32 (m, 1 H), 1.30 - 1.19 (m, 2 H), 1.16 (s, 3 H), 0.82 (d, *J* = 6.9 Hz, 3 H), 0.37 (dd, *J* = 2.8, 6.9 Hz, 1 H), 0.25 (s, 3 H), 0.14 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 210.1, 183.3, 139.0, 135.1, 129.3, 66.3, 46.4, 41.4, 39.5, 38.6, 37.8, 35.8, 35.4, 32.2, 31.8, 31.5, 23.6, 22.2, 12.5, 1.82, –1.89. **HRMS(ES+)** *m/z* 345.2259 [$(M+H)^+$; calcd for $C_{21}H_{33}O_2Si$: 345.2250].



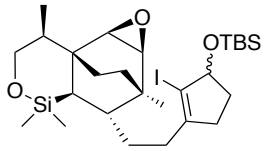

**Epoxide (–)-2.29:** Enone (–)-**2.20** (500 mg, 1.45 mmol) was dissolved in $CH_2Cl_2$ (7.5 mL) and $NaHCO_3$ (243 mg, 2.90 mmol) was added. The solution was cooled to 0 °C and *m*-CPBA (70%, 551 mg, 2.18 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 0.5 h and for an additional 1 h at room temperature. The suspension was diluted with $CH_2Cl_2$ (20 mL), saturated aqueous $Na_2S_2O_3$ (15 mL), and saturated

aqueous $NaHCO_3$ (15 mL each), and the biphasic mixture was vigorously stirred for 45 minutes. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2:1 → 1:1 hexanes/EtOAc) to afford the title compound (448 mg, 86%) as a colorless oil. $[\alpha]_D^{20}$ –4.3 (*c* 0.9 $CHCl_3$). **IR** (neat) 2957, 2866, 1707, 1676, 1615, 1251 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.94 (s, 1 H), 3.70 (dd, *J* = 4.6, 11.5 Hz, 1 H), 3.60 (t, *J* = 11.5 Hz, 1 H), 2.98 (d, *J* = 5.0 Hz, 1 H), 2.91 (dd, *J* = 1.2, 5.0 Hz, 1 H), 2.58 (dd, *J* = 3.0, 4.4 Hz, 2 H), 2.47 - 2.35 (m, 3 H), 2.33 - 2.21 (m, 1 H), 1.92 - 1.84 (m, 1 H), 1.80 (ddd, *J* = 4.7, 6.9, 11.4 Hz, 1 H), 1.65 - 1.49 (m, 3 H), 1.45 - 1.33 (m, 3 H), 1.14 (s, 3 H), 1.01 (dt, *J* = 3.9, 11.9 Hz, 1 H), 0.87 (d, *J* = 6.9 Hz, 2 H), 0.65 (dd, *J* = 2.6, 5.9 Hz, 1 H), 0.24 (s, 3 H), 0.19 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 209.8, 182.2, 129.6, 66.3, 60.0, 56.5, 45.0, 41.2, 40.1, 35.9, 35.7, 35.4, 32.7, 32.5, 32.2, 31.8, 23.8, 19.2, 12.2, 2.21, -1.00. **HRMS(ES+)** *m/z* 361.2199 [$(M+H)^+$; calcd for $C_{21}H_{33}O_3Si$: 361.2199].



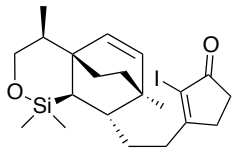

**Enone (+)-2.3:** To a solution of enone (–)-**2.29** (447 mg, 1.24 mmol) in pyridine (2.5 mL) and $CCl_4$ (2.5 mL) was added $I_2$ (1.88 g, 7.44 mmol) in one portion at room temperature. The dark brown solution was stirred for 8 h and quenched with saturated aqueous $Na_2S_2O_3$ (5 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (5 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel

(2:1 hexanes/EtOAc) to afford the title compound (519 mg, 86%) as a colorless oil. $[\alpha]_D^{20}$ +1.3 (*c* 0.3 $CHCl_3$). **IR** (neat) 2957, 2919, 2866, 1707, 1640, 1598 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.71 (dd, *J* = 4.6, 11.7 Hz, 1 H), 3.61 (t, *J* = 11.7 Hz, 1 H), 2.98 (d, *J* = 5.0 Hz, 1 H), 2.92 (d, *J* = 5.0 Hz, 1 H), 2.81 - 2.69 (m, 2 H), 2.62 - 2.51 (m, 3 H), 2.39 (dt, *J* = 4.1, 12.7 Hz, 1 H), 1.83 (ddd, *J* = 4.7, 6.9, 11.4 Hz, 1 H), 1.76 (tt, *J* = 4.1, 13.0 Hz, 1 H), 1.61 (dt, *J* = 3.1, 11.8 Hz, 1 H), 1.55 (tt, *J* = 3.0, 11.9 Hz, 1 H), 1.46 (dt, *J* = 4.2, 7.2 Hz, 1 H), 1.43 - 1.37 (m, 1 H), 1.35 (ddd, *J* = 5.0, 7.7, 12.9 Hz, 1 H), 1.18 (s, 3 H), 1.03 (dt, *J* = 3.8, 11.8 Hz, 1 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.74 (dd, *J* = 2.5, 6.6 Hz, 1 H), 0.26 (s, 3 H), 0.25 (s, 3 H). **$^{13}$C NMR** (125 MHz, $C_6D_6$) δ 201.2, 180.3, 103.6, 66.2, 58.7, 55.8, 45.3, 41.2, 40.1, 35.8, 35.7, 34.8, 32.9, 32.6, 31.8, 31.3, 23.5, 19.4, 12.0, 2.47, –1.06. **HRMS(ES+)** *m/z* 487.1151 [$(M+H)^+$; calcd for $C_{21}H_{32}IO_3Si$: 487.1166].



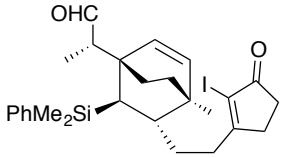

**Vinyl Iodide 2.30:** To a solution of enone (+)-**2.3** (430 mg, 0.884 mmol) in MeOH (5 mL) was added $CeCl_3 \bullet 7H_2O$ (822 mg, 2.21 mmol) and the resulting suspension was cooled to 0 °C. Sodium borohydride (83.5 mg, 2.21 mmol) was carefully added and the reaction mixture was allowed to warm to room temperature. Water (5 mL) was added, followed by EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to afford the corresponding allylic alcohol (353 mg, 82%) as a colorless oil.

To a solution of the allylic alcohol (10.4 mg, 0.0213 mmol) in $CH_2Cl_2$ (0.2 mL) were added DMAP (one small crystal) and $Et_3N$ (15 μL, 0.106 mmol) sequentially. TBSCl (4.8 mg, 0.0319 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with $CH_2Cl_2$ (5 mL) and water (5 mL) was added. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (15:1 hexanes/EtOAc) to afford the title compound (11.9 mg, 93%, 1:1 d.r.) as a colorless oil. **IR** (neat) 2956, 2929, 2857, 1639, 1461, 1250, 1113 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) Diagnostic signals: δ 4.76 - 4.69 (m, 1 H), 3.72 - 3.66 (m, 1 H), 3.63 - 3.56 (m, 1 H), 2.98 (d, $J$ = 5.0 Hz, 1 H), 2.90 (d, $J$ = 5.2 Hz, 1 H), 0.93 (s, 9 H), 0.16 (s, 3 H), 0.13 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 150.1, 150.1, 100.2, 100.1, 82.7, 66.3, 59.3, 59.2, 56.7, 45.2, 45.1, 41.2, 40.1, 35.7, 35.7, 35.6, 33.4, 33.2, 33.0, 32.9, 32.7, 32.0, 32.0, 26.1, 23.8, 23.7, 19.3, 18.5, 12.2, 2.3, 2.3, –1.0, –4.2, –4.3. **HRMS(ES+)** *m/z* 625.2005 [$(M+Na)^+$; calcd for $C_{27}H_{47}IO_3Si_2Na$: 625.2006].




**Iodide (–)-2.37:** Triphenylphosphine (179 mg, 0.683 mmol) was dissolved in THF (1.7 mL) and TBSOTf (0.16 mL, 0.683 mmol) was added, followed by dropwise addition of 2-iodo-2-cyclopentenone (142 mg, 0.683 mmol) in THF (0.5 mL) at room temperature. After 45 min, TLC indicated complete consumption of the enone, and the solution was cooled to –78 °C. In a separate flask, *n*-BuLi (1.89 M/hexanes, 0.36 mL, 0.683 mmol)

was added to a solution of *i*-$Pr_2NH$ (95 μL, 0.683 mmol) in THF (1 mL) at –78 °C. After stirring for 0.5 h at this temperature, the resulting solution of LDA was transferred to the solution of the Wittig salt dropwise via cannula, producing a deep black solution of the ylide. After stirring for an additional 0.5 h, a solution of the aldehyde (–)-**2.28** (95 mg, 0.341 mmol) in THF (0.5 mL) was added by syringe. The reaction mixture was allowed to warm to room temperature and 1 M HCl (4 mL) was added. The reaction mixture was vigorously stirred for 1 h and the layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 2) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5:1 hexanes/EtOAc) to afford the title compound (145 mg, 90%) as a colorless oil. $[\alpha]_D^{20}$ –6.5 (*c* 0.31 $CHCl_3$). **IR** (neat) 3028, 2950, 2918, 2854, 1709, 1641, 1598 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.21 (d, *J* = 8.5 Hz, 1 H), 5.82 (d, *J* = 8.3 Hz, 1 H), 3.71 (app d, *J* = 7.9 Hz, 2 H), 2.73 - 2.68 (m, 2 H), 2.59 - 2.54 (m, 2 H), 2.37 (dt, *J* = 5.1, 12.7 Hz, 2 H), 2.07 (sxt, *J* = 7.3 Hz, 1 H), 1.72 (ddd, *J* = 3.2, 9.7, 12.7 Hz, 1 H), 1.53 (ddd, *J* = 4.2, 6.7, 13.9 Hz, 1 H), 1.49 - 1.43 (m, 1 H), 1.39 (ddd, *J* = 4.4, 10.5, 11.9 Hz, 1 H), 1.28 - 1.18 (m, 2 H), 1.22 (s, 3 H), 1.15 (ddd, *J* = 3.0, 4.2, 12.3 Hz, 1 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.47 (dd, *J* = 2.9, 7.0 Hz, 1 H), 0.27 (s, 3 H), 0.20 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 203.6, 183.5, 139.2, 135.0, 102.3, 66.3, 46.4, 41.4, 39.5, 38.5, 37.8, 35.9, 33.9, 33.1, 32.5, 31.6, 23.5, 22.2, 12.4, 2.0, –2.0. **HRMS(ES+)** *m/z* 471.1206 [$(M+H)^+$; calcd for $C_{21}H_{32}IO_2Si$: 471.1216].

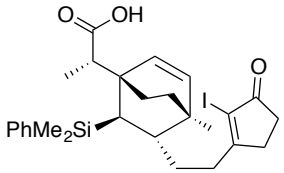


**Aldehyde (+)-2.39:** To a solution of enone (–)-**2.37** (518 mg, 1.10 mmol) in MeOH (6 mL) was added $CeCl_3 \bullet 7H_2O$ (491 mg, 1.32 mmol) and the resulting suspension was cooled to 0 °C. Sodium borohydride (104 mg, 2.75 mmol) was carefully added and the reaction mixture was allowed to warm to room temperature. Water (5 mL) was added and the mixture was diluted with EtOAc (10 mL). The turbid mixture was transferred to a separatory funnel and 1 M HCl (5 mL) was added. The resulting clear layers were separated and the aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The product was used directly in the next step without purification.

To a solution of the allylic alcohol (518 mg, 1.10 mmol) in THF (8 mL) was added PhLi (2 M/$Bu_2O$, 0.83 mL, 1.65 mmol) dropwise at room temperature. After stirring for 15 minutes, the reaction was quenched by the addition of saturated aqueous $NH_4Cl$ (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (3:1 hexanes/EtOAc) to afford the corresponding diol (453 mg, 75% over 2 steps) as a colorless oil.

To a solution of the diol (253 mg, 0.460 mmol) in $CH_2Cl_2$ (2 mL) and MeCN (1 mL) was added NMO (118 mg, 1.01 mmol), followed by TPAP (8 mg, 0.023 mmol) at room temperature. The reaction mixture was stirred for 2 h and the solvent was removed *in vacuo*. The residue was dissolved in $CH_2Cl_2$ and filtered through a short pad of silica gel. Evaporation of the solvent afforded the title compound as a colorless oil, which was used directly in the next step without purification. $[\alpha]_D^{20}$ +21.0 (*c* 0.39 $CHCl_3$). **IR** (neat) 2949, 2932, 2860, 2726, 1711, 1642, 1596, 1427, 1250, 1110 $cm^{-1}$. **$^1$H NMR** (500 MHz,

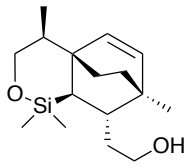
$CDCl_3$) δ 9.77 (d, *J* = 3.4 Hz, 1 H), 7.63 - 7.55 (m, 2 H), 7.40 - 7.32 (m, 3 H), 6.30 (d, *J* = 8.5 Hz, 1 H), 5.97 (d, *J* = 8.5 Hz, 1 H), 2.54 - 2.47 (m, 3 H), 2.46 - 2.43 (m, 1 H), 2.43 - 2.35 (m, 2 H), 1.97 (dt, *J* = 5.2, 13.0 Hz, 1 H), 1.70 - 1.62 (m, 2 H), 1.39 - 1.30 (m, 1 H), 1.30 - 1.25 (m, 1 H), 1.27 (s, 3 H), 1.24 - 1.20 (m, 1 H), 1.17 - 1.11 (m, 2 H), 1.10 - 1.05 (m, 1 H), 1.08 (d, *J* = 6.7 Hz, 3 H), 1.05 - 0.98 (m, 2 H), 0.89 (dd, *J* = 2.7, 5.6 Hz, 1 H), 0.52 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 205.6, 203.7, 183.6, 139.7, 137.7, 135.0, 134.1, 129.3, 128.1, 101.9, 51.8, 47.6, 43.1, 38.3, 37.6, 35.9, 34.6, 33.4, 33.0, 32.3, 31.9, 24.2, 10.8, –0.4, –1.9. **HRMS(ES+)** *m/z* 569.1326 [$(M+Na)^+$; calcd for $C_{27}H_{35}IO_2SiNa$: 569.1349].




**Acid (+)-2.32:** To a solution of aldehyde (+)-**2.3** (252 mg, 0.460 mmol) and 2-methyl-2-butene (0.48 mL, 4.60 mmol) in *t*-BuOH (4 mL) and $H_2O$ (1 mL) was added a solution of $NaClO_2$ (207 mg, 2.30 mmol) and $Na_2H_2PO_4$ (273 mg, 2.30) in $H_2O$ (1 mL) at room temperature. The reaction mixture was stirred for 1 h and quenched with pH 7 buffer (5 mL). The reaction mixture was diluted with $CH_2Cl_2$ (10 mL) and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (10 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to afford the title compound (207 mg, 80% over 2 steps) as an amorphous solid. $[\alpha]_D^{20}$ +15.6 (*c* 0.21 $CHCl_3$). **IR** (neat) 3213, 2950, 2860, 1705, 1646, 1595, 1427, 1322, 1250, 1109 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 3.0, 6.3 Hz, 2 H), 7.38 - 7.32 (m, 3 H), 6.51 (d,

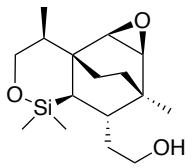
$J$ = 8.5 Hz, 1 H), 5.87 (d, $J$ = 8.7 Hz, 1 H), 2.68 (q, $J$ = 6.9 Hz, 1 H), 2.51 - 2.44 (m, 2 H), 2.40 (ddd, $J$ = 4.8, 10.3, 12.9 Hz, 2 H), 1.96 (dt, $J$ = 5.1, 12.9 Hz, 1 H), 1.66 - 1.57 (m, 2 H), 1.34 - 1.28 (m, 1 H), 1.27 - 1.25 (m, 1 H), 1.24 (s, 3 H), 1.20 - 1.14 (m, 2 H), 1.13 (d, $J$ = 6.9 Hz, 3 H), 1.07 - 0.98 (m, 2 H), 0.87 (dd, $J$ = 1.8, 5.7 Hz, 1 H), 0.51 (s, 3 H), 0.49 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 203.9, 183.9, 180.1, 139.7, 136.0, 135.7, 134.1, 129.2, 128.1, 101.8, 47.9, 44.8, 43.2, 37.7, 37.3, 35.6, 34.5, 33.4, 33.0, 32.3, 31.2, 24.2, 13.6, –0.6, –1.9. **HRMS(ES+)** *m/z* 561.1326 [$(M–H)^+$; calcd for $C_{27}H_{34}IO_3Si$: 561.1322].

## 5-3: Experimental Procedures Relevant to Chapter 3



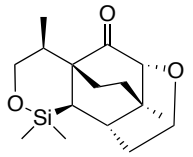

**Alcohol (–)-3.1:** Aldehyde (–)-**2.28** (9.0 g, 32.3 mmol) was dissolved in EtOH (150 mL) and $NaBH_4$ (1.46 g, 38.8 mmol) was added portion wise at room temperature. Upon completion, water was added carefully to quench excess hydride, the solution was concentrated to ca. 40 mL, and the aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash choromotography on silica gel (4:1 hexanes/EtOAc) to afford the title compound (9.0 g, 99%) as a colorless oil. $[\alpha]_D^{20}$ –55.6 (*c* 0.46 $CHCl_3$). **IR** (neat) 3408, 3029, 2950, 2872, 1645, 1250, 1104, 1067 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.19 (d, $J$ = 8.3 Hz, 1 H), 5.79 (d, $J$ = 8.3 Hz, 1 H), 3.69 (d, $J$ = 7.9 Hz, 2 H), 3.61 - 3.45 (m, 2 H), 2.01 (qd, $J$ = 7.3, 14.8 Hz, 1 H), 1.74 - 1.64 (m, 2 H), 1.48 (dt, $J$ = 4.5, 7.0 Hz, 1 H), 1.40 - 1.33 (m, 1 H), 1.22 (dt, $J$ = 4.0, 12.0, 1 H), 1.18

- 1.11 (m, 3 H), 1.16 (s, 3 H), 0.81 (d, $J$ = 6.9 Hz, 3 H), 0.35 (dd, $J$ = 2.9, 6.6 Hz, 1 H), 0.25 (s, 3 H), 0.18 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 139.2, 135.1, 66.4, 61.1, 43.1, 41.4, 39.6, 38.9, 38.2, 37.7, 35.6, 23.7, 22.3, 12.5, 1.54, –1.86. **HRMS(ES+)** *m/z* 281.1944 [$(M+H)^+$; calcd for $C_{16}H_{29}O_2Si$: 281.1937].




**Epoxide (–)-3.2:** To a cooled (0 °C) solution of alkene (–)-**3.1** (9.0 g, 32.1 mmol) in $CH_2Cl_2$ (200 mL) was added $NaHCO_3$ (5.4 g, 64.2 mmol), followed by *m*-CPBA (8.6 g, 38.6 mmol). The reaction mixture was allowed to warm to room temperature and stir for 1 h. Saturated aqueous $Na_2S_2O_3$ (20 mL) and saturated aqueous $NaHCO_3$ (20 mL) were added, and the mixture was vigorously stirred for an additional 0.5 h. After diluting with water (30 mL), the layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (30 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to afford the title compound (6.36 g, 70%) as a colorless oil. $[\alpha]_D^{20}$ – 7.4 (*c* 1.78 $CHCl_3$). **IR** (neat) 3440, 2959, 2919, 2869, 1254, 1120, 1085, 1055 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.72 - 3.63 (m, 2 H), 3.63 - 3.50 (m, 2 H), 2.97 (d, $J$ = 4.8 Hz, 1 H), 2.89 (dd, $J$ = 1.0, 5.0 Hz, 1 H), 1.94 (tdd, $J$ = 3.9, 7.8, 17.2 Hz, 1 H), 1.81 - 1.73 (m, 1 H), 1.60 - 1.44 (m, 3 H), 1.41 - 1.30 (m, 3 H), 1.11 (s, 3 H), 1.01 (dt, $J$ = 4.4, 12.5 Hz, 1 H), 0.86 (d, $J$ = 6.9 Hz, 3 H), 0.63 (dd, $J$ = 2.5, 6.4 Hz, 1 H), 0.23 (s, 3 H), 0.21 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 66.3, 61.2, 59.0, 56.6, 41.2, 40.9, 40.0, 37.7, 35.8,

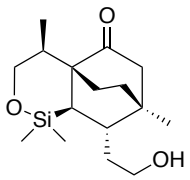
35.2, 32.3, 23.8, 19.2, 12.2, 1.60, –1.08. **HRMS(ES+)** *m/z* 297.1899 [$(M+H)^+$; calcd for $C_{16}H_{29}O_3Si$: 297.1886].




**Ketone (+)-3.3:** Epoxide (–)-**3.2** (6.36 g, 21.4 mmol) was dissolved in $CH_2Cl_2$ (150 mL) and cooled to 0 °C. PPTS (268 mg, 1.07 mmol) was added and the resulting solution was stirred at 0 °C for 1 h. After warming to room temperature, the solution was washed with water (30 mL), and the aqueous layer was extracted with $CH_2Cl_2$ (20 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was used without purification.

The resulting alcohol was dissolved in $CH_2Cl_2$ (150 mL) and cooled to 0 °C. $NaHCO_3$ (3.59 g, 42.8 mmol) was added, followed by Dess-Martin periodinane (10.8 g, 25.7 mmol). The reaction mixture was stirred at room temperature for 1 h, then quenched with saturated aqueous $Na_2S_2O_3$ (30 mL). After stirring for 15 min, the layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (20 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (4:1 hexanes/EtOAc) to afford the title compound (4.2 g, 67% over 2 steps) as a colorless oil. $[\alpha]_D^{20}$ +98.0 (*c* 2.52 $CHCl_3$). **IR** (neat) 2950, 2863, 1720, 1473, 1253, 1137, 1103 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.71 - 3.61 (m, 3 H), 3.55 (dt, *J* = 3.6, 12.8 Hz, 1 H), 3.50 (d, *J* = 1.8 Hz, 1 H), 2.33 - 2.21 (m, 2 H), 1.98 - 1.91 (m, 1 H), 1.68 - 1.51 (m, 4 H), 1.15 (s, 3 H), 0.89 (td, *J* = 3.2, 13.7 Hz, 1 H), 0.77 (d, *J* = 6.9 Hz, 3 H), 0.72 (dd, *J* = 1.8, 4.6 Hz, 1 H), 0.34 (s, 3 H), 0.11 (s, 3 H). **$^{13}$C NMR** (125

MHz, $CDCl_3$) δ 211.0, 80.5, 65.8, 58.1, 48.7, 36.0, 35.1, 34.1, 31.7, 30.9, 29.5, 22.4, 17.5, 12.0, –0.60, –2.05. **HRMS(ES+)** *m/z* 295.1728 [$(M+H)^+$; calcd for $C_{16}H_{27}O_3Si$: 295.1729].

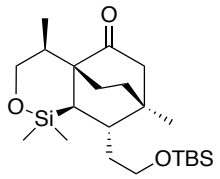



**Alcohol (+)-3.7:** The following reaction was run in two batches, which were combined for purification.

Batch 1 (1.56 g (+)-**3.3**, 5.31 mmol): A 1-L flask was charged with $Sm^0$ powder (3.18 g, 21.2 mmol) and the flask was flushed with nitrogen for 5 min. The flask was wrapped with aluminum foil and THF (212 mL) was added. The suspension was stirred vigorously while freshly distilled $CH_2I_2$ (1.7 mL, 21.2 mmol) was added dropwise in the dark. The suspension changed gradually to a teal, then deep blue solution within 0.5 h. The solution was stirred for an additional 4 h before a solution of the ketone (1.56 g, 5.31 mmol) in THF (6 mL) and MeOH (3 mL) was added dropwise at room temperature via cannula. The reaction mixture was rapidly poured into a vigorously stirring solution of saturated aqueous $NaHCO_3$ (30 mL) and the resulting suspension was filtered through a pad of celite. The layers were separated and the aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the first batch of (+)-**3.7**.

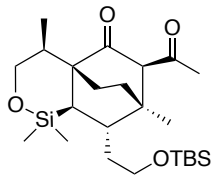
Batch 2 (517 mg (+)-**3.3**, 1.76 mmol): To a rapidly stirring suspension of $Sm^0$ powder (1.05 g, 7.03 mmol) in THF (70 mL) was added freshly distilled $CH_2I_2$ (0.56 mL, 7.03 mmol) in the dark. The suspension gradually turned to a deep blue solution within 0.5 h

and vigorous stirring was continued for an additional 4 h. A solution of ketone (+)-**3.3** (517 mg, 1.76 mmol) in THF (2 mL) and MeOH (1 mL) was added dropwise via cannula. An identical workup as above provided another batch of (+)-**3.7**. The combined batches were purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to afford the title compound (2.32 g, 82%) as a white solid. Melting point 103-105 °C. $[\alpha]_D^{20}$ +62.9 (*c* 0.94 $CHCl_3$). **IR** (neat) 3436, 2953, 2876, 1709, 1251 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.71 - 3.59 (m, 3 H), 3.58 - 3.51 (m, 1 H), 2.36 (dd, *J* = 2.5, 18.3 Hz, 1 H), 2.25 (tt, *J* = 6.7, 11.9 Hz, 1 H), 2.04 (d, *J* = 18.2 Hz, 1 H), 2.01 (ddd, *J* = 3.2, 10.5, 13.9 Hz, 1 H), 1.88 (dtd, *J* = 4.6, 7.5, 11.9 Hz, 1 H), 1.73 (dddd, *J* = 2.0, 7.1, 10.1, 13.1 Hz, 1 H), 1.67 - 1.56 (m, 2 H), 1.55 - 1.49 (m, 1 H), 1.35 (br s, 1 H), 1.23 (ddd, *J* = 6.7, 13.9, 20.4 Hz, 1 H), 1.00 (s, 3 H), 0.72 (d, *J* = 6.7 Hz, 3 H), 0.65 (dd, *J* = 2.0, 5.9 Hz, 1 H), 0.35 (s, 3 H), 0.21 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 213.7, 65.5, 61.0, 48.5, 46.6, 38.3, 36.8, 36.4, 36.3, 34.8, 25.2, 18.4, 12.2, 0.6, –1.3. **HRMS(ES+)** *m/z* 297.1890 [$(M+H)^+$; calcd for $C_{16}H_{29}O_3Si$: 297.1886].




**Ketone (+)-3.6:** A solution of alcohol (+)-**3.7** (2.86 g, 9.66 mmol) and imidazole (1.97 g, 29.0 mmol) in DMF (39 mL) was cooled to 0 °C. TBSCl (1.74 g, 11.6 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was diluted with EtOAc (30 mL) and quenched by the addition of water (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in*

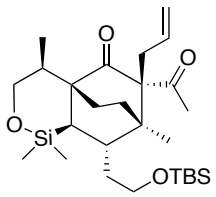
*vacuo*. The residue was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc) to afford the title compound (3.84 g, 97%) as a colorless oil. $[\alpha]_D^{20}$ +22.3 (*c* 0.63 $CHCl_3$). **IR** (neat) 2953, 2935, 2879, 2859, 1713, 1466, 1252, 1099, 1070, 834 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.67 - 3.56 (m, 3H), 3.54 - 3.45 (m, 1 H), 2.34 (dd, *J* = 2.6, 18.4 Hz, 1 H), 2.27 - 2.17 (m, 1 H), 2.02 - 1.96 (m, 1 H), 2.01 (dd, *J* = 1.4, 18.6 Hz, 1 H), 1.84 - 1.75 (m, 1 H), 1.75 - 1.66 (m, 1 H), 1.65 - 1.51 (m, 3 H), 1.13 (tdd, *J* = 5.9, 7.9, 13.7 Hz, 1 H), 0.96 (s, 3 H), 0.87 (s, 9 H), 0.71 (d, *J* = 6.7 Hz, 3 H), 0.60 (dd, *J* = 2.2, 6.1 Hz, 1 H), 0.32 (s, 3 H), 0.20 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 213.8, 65.5, 61.1, 48.4, 46.6, 37.8, 37.0, 36.4, 36.2, 34.9, 34.8, 26.1, 25.3, 18.5, 18.4, 12.2, 0.51, –1.41, –5.06, –5.12. **HRMS(ES+)** *m/z* 411.2753 $[(M+H)^+$; calcd for $C_{22}H_{43}O_3Si_2$: 411.2751].



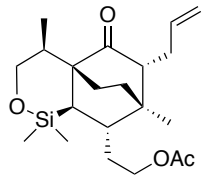

**Diketone (+)-3.8:** To a cooled (–78 °C) solution of diisopropylamine (0.85 mL, 6.14 mmol) in THF (25 mL) was added *n*-BuLi (2.5M/hexanes, 2.45 mL, 6.14 mmol) dropwise. After stirring for 0.5 h, a solution of ketone (+)-**3.6** (1.26 g, 3.07 mmol) in THF (9 mL) was added dropwise via cannula. The resulting solution was stirred for 0.5 h at –78 °C before MeCHO (5M/THF, 1.35 mL, 6.73 mmol) was added dropwise by syringe. The reaction was quenched at –78 °C with saturated aqueous $NH_4Cl$ (10 mL). Upon warming to room temperature, water (10 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers

were dried over $MgSO_4$ and concentrated *in vacuo*. The product was used without purification.

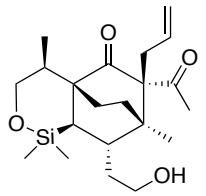
The resulting β-hydroxy ketone was dissolved in $CH_2Cl_2$ (20 mL) and cooled to 0 °C. Sodium bicarbonate (564 mg, 6.72 mmol) was added, followed by Dess-Martin periodinane (1.84 g, 4.36 mmol). The reaction mixture was stirred at 0 °C for 15 min, then at room temperature for 0.5 h. Upon completion, saturated aqueous $Na_2S_2O_3$ (10 mL) was added and the biphasic mixture was stirred vigorously for 15 min. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (15 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (12:1 hexanes/EtOAc) to afford the title compound (1.37 g, 91% over 2 steps) as a colorless oil. $[\alpha]_D^{20}$ +57.8 (*c* 0.8 $CHCl_3$). **IR** (neat) 2954, 2926, 2879, 2857, 1722, 1698, 1253, 1099 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.70 - 3.57 (m, 3 H), 3.53 (d, *J* = 1.2 Hz, 1 H), 3.49 (ddd, *J* = 5.7, 8.3, 10.3 Hz, 1 H), 2.28 (s, 3 H), 2.25 - 2.11 (m, 2 H), 1.96 (ddd, *J* = 2.4, 11.1, 14.1 Hz, 1 H), 1.92 - 1.79 (m, 2 H), 1.52 (ddd, *J* = 4.0, 5.9, 8.5 Hz, 1 H), 1.38 (ddt, *J* = 1.8, 7.7, 11.1 Hz, 1 H), 1.13 (tdd, *J* = 5.5, 8.5, 10.9 Hz, 1 H), 1.04 (s, 3 H), 0.88 (s, 9 H), 0.69 (d, *J* = 6.7 Hz, 3 H), 0.58 (dd, *J* = 2.2, 5.9 Hz, 1 H), 0.33 (s, 3 H), 0.20 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 208.7, 205.0, 66.5, 65.4, 60.7, 48.6, 39.7, 38.7, 36.8, 36.0, 35.0, 33.6, 31.0, 26.0, 23.5, 18.4, 18.1, 12.0, 0.43, –1.30, –5.08, –5.13. **HRMS(ES+)** *m/z* 453.2858 $[(M+H)^+$; calcd for $C_{24}H_{45}O_4Si_2$: 453.2856].



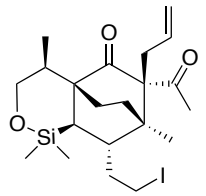

**Diketone (–)-3.10:** To a cooled (0 °C) solution of diketone (+)-**3.8** (1.37 g, 3.03 mmol) and $Pd(PPh_3)_4$ (174 mg, 0.151 mmol) in THF (16 mL) was added sodium hydride (60 wt% in mineral oil, 145 mg, 3.63 mmol), followed by dropwise addition of allyl acetate (0.39 mL, 3.63 mmol). The reaction mixture was warmed to room temperature and stirred for 0.5 h. The reaction was quenched by addition of saturated aqueous $NH_4Cl$ (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (15:1 hexanes/EtOAc) to afford the title compound (1.41 g, 95%) as a colorless oil. $[\alpha]_D^{20}$ –1.8 (*c* 0.94 $CHCl_3$). **IR** (neat) 2955, 2927, 2881, 2857, 1699, 1469, 1253, 1097 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.72 (tdd, *J* = 7.1, 9.9, 17.0 Hz, 1 H), 5.04 (td, *J* = 0.9, 10.0 Hz, 1 H), 4.94 (dd, *J* = 1.7, 16.9 Hz, 1 H), 3.70 - 3.56 (m, 2 H), 3.49 (t, *J* = 6.1 Hz, 2 H), 2.85 - 2.76 (m, 1 H), 2.31 (tdd, *J* = 6.9, 11.7, 13.5 Hz, 1 H), 2.24 (s, 3 H), 2.14 (dd, *J* = 7.0, 13.6 Hz, 1 H), 2.05 - 1.88 (m, 2 H), 1.73 - 1.57 (m, 3 H), 1.33 (ddd, *J* = 6.2, 11.9, 14.0 Hz, 1 H), 1.07 (s, 3 H), 1.06 - 0.99 (m, 1 H), 0.87 (s, 9 H), 0.75 (d, *J* = 6.7 Hz, 3 H), 0.73 (dd, *J* = 2.0, 8.5, 1 H), 0.35 (s, 3 H), 0.24 (s, 3 H), 0.01 (s, 6 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 210.8, 208.9, 133.3, 118.6, 66.9, 65.0, 62.6, 49.1, 43.4, 40.5, 38.6, 38.3, 35.5, 35.3, 33.9, 33.2, 26.2, 21.0, 18.6, 18.0, 12.6, 0.91, –1.71, –5.09, –5.16. **HRMS(ES+)** *m/z* 493.3172 [$(M+H)^+$; calcd for $C_{27}H_{49}O_4Si_2$: 493.3169].



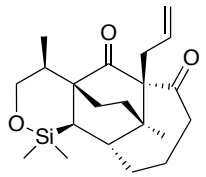

**Acetate (+)-3.12:** To a solution of TBS ether (–)-**3.10** (12 mg, 0.0243 mmol) in THF (0.3 mL) was added TBAF (1 M/THF, 36 μL, 0.0364 mmol) at room temperature. The reaction mixture was stirred for 12 h and quenched by the addition of saturated aqueous $Na_2S_2O_3$ (1 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (8:1 hexanes/EtOAc) to afford the title compound (4 mg, 44%) as a colorless oil. $[\alpha]_D^{20}$ +20.7 (*c* 0.27 $CHCl_3$). **IR** (neat) 2956, 2922, 2877, 2858, 1740, 1707, 1641, 1469, 1367, 1235, 1072 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.91 (tdd, *J* = 6.8, 10.1, 16.9 Hz, 1 H), 5.05 - 4.99 (m, 2 H), 4.11 (ddd, *J* = 5.9, 7.4, 11.0 Hz, 1 H), 3.89 (td, *J* = 7.3, 11.0 Hz, 1 H), 3.67 (dd, *J* = 4.8, 11.7 Hz, 1 H), 3.64 - 3.57 (m, 1 H), 2.43 - 2.34 (m, 1 H), 2.30 - 2.16 (m, 3 H), 2.03 (s, 3 H), 2.01 - 1.92 (m, 2 H), 1.82 (ddd, *J* = 2.2, 11.3, 13.7 Hz, 1 H), 1.74 - 1.65 (m, 1 H), 1.45 - 1.37 (m, 2 H), 1.26 (dt, *J* = 7.1, 13.7 Hz, 1 H), 0.99 (s, 3 H), 0.69 (d, *J* = 6.7 Hz, 3 H), 0.61 (dd, *J* = 2.1, 6.0 Hz, 1 H), 0.34 (s, 3 H), 0.18 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 214.2, 171.0, 137.3, 116.0, 65.4, 63.3, 52.1, 48.4, 40.8, 38.4, 36.5, 34.8, 32.7, 32.0, 30.6, 23.5, 21.1, 18.1, 12.2, 0.6, –1.3. **HRMS(ES+)** *m/z* 401.2125 [$(M+Na)^+$; calcd for $C_{21}H_{34}O_4SiNa$: 401.2124].




**Alcohol (–)-3.11:** To a cooled (0 °C) solution of silyl ether (–)-**3.10** (3.57 g, 7.25 mmol) in MeOH (30 mL) was added *p*-toluenesulfonic acid (275 mg, 1.45 mmol). The reaction mixture was stirred at 0 °C for 0.5 h, then allowed to warm to room temperature. Ethyl acetate (20 mL) was added and the solution was washed with water (20 mL). The aqueous layer was extracted with EtOAc (20 mL x 2) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to afford the title compound (2.52 g, 92%) as a white solid. Melting point 89-91 °C. $[\alpha]_D^{20}$ –4.5 (*c* 0.7 $CHCl_3$). **IR** (neat) 3442, 2956, 2924, 2882, 1697, 1354, 1253, 1053 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.73 (tdd, *J* = 7.1, 10.0, 17.0 Hz, 1 H), 5.04 (td, *J* = 0.7, 10.1 Hz, 1 H), 4.95 (dd, *J* = 1.5, 16.9 Hz, 1 H), 3.73 - 3.43 (m, 4 H), 2.80 (dd, *J* = 7.3, 13.7 Hz, 1 H), 2.32 (ddd, *J* = 4.9, 6.6, 11.3 Hz, 1 H), 2.25 (s, 3 H), 2.15 (dd, *J* = 6.7, 13.5 Hz, 1 H), 2.05 - 1.88 (m, 2 H), 1.75 - 1.63 (m, 2 H), 1.56 (ddd, *J* = 4.1, 5.5, 9.3 Hz, 1 H), 1.38 - 1.26 (m, 2 H), 1.11 - 1.05 (m, 1 H), 1.08 (s, 3 H), 0.78 (dd, *J* = 2.0, 9.0, 1 H), 0.76 (d, *J* = 6.5, 3 H), 0.36 (s, 3 H), 0.25 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 210.6, 209.0, 133.3, 118.6, 66.9, 64.9, 62.8, 49.1, 43.3, 41.1, 38.6, 38.1, 35.7, 35.3, 33.8, 33.0, 20.7, 17.9, 12.6, 0.98, –1.72. **HRMS(ES+)** *m/z* 379.2308 [$(M+H)^+$; calcd for $C_{21}H_{35}O_4Si$: 379.2305].



**Iodide (–)-3.5:** To a cooled (0 °C) solution of alcohol (–)-**3.11** (2.52 g, 6.66 mmol) in THF (25 mL) was added $PPh_3$ (2.09 g, 8.00 mmol), imidazole (993 mg, 14.6 mmol), and $I_2$ (2.02 g, 8.00 mmol) sequentially. The cold bath was removed and the brown solution was stirred at room temperature for 10 min. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (15 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (15 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc) to afford the title compound (3.17 g, 97%) as a colorless oil. $[\alpha]_D^{20}$ –1.6 (*c* 0.7 $CHCl_3$). **IR** (neat) 2956, 2924, 2882, 2860, 1698, 1353, 1253, 1169, 1101 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.72 (tdd, *J* = 7.1, 10.0, 17.0 Hz, 1 H), 5.05 (td, *J* = 0.9, 10.0 Hz, 1 H), 4.96 (dd, *J* = 1.7, 16.9 Hz, 1 H), 3.70 - 3.58 (m, 2 H), 3.17 - 3.06 (m, 2 H), 2.78 (dd, *J* = 7.5, 13.7 Hz, 1 H), 2.31 (ddd, *J* = 4.8, 6.6, 11.4 Hz, 1 H), 2.24 (s, 3 H), 2.21 - 2.15 (m, 1 H), 2.06 - 1.88 (m, 3 H), 1.68 (dddd, *J* = 2.2, 6.1, 11.5, 13.9 Hz, 1 H), 1.53 (ddd, *J* = 4.6, 5.7, 8.9 Hz, 1 H), 1.43 - 1.32 (m, 2 H), 1.14 (s, 3 H), 0.76 (d, *J* = 6.7 Hz, 3 H), 0.70 (dd, *J* = 2.2, 8.7 Hz, 1 H), 0.43 (s, 3 H), 0.27 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 210.3, 208.7, 133.0, 118.8, 67.0, 64.9, 49.1, 46.6, 43.2, 39.1, 38.4, 35.3, 35.0, 33.8, 33.1, 21.0, 18.0, 12.6, 6.79, 1.33, –1.11. **HRMS(ES+)** *m/z* 489.1317 [$(M+H)^+$; calcd for $C_{21}H_{34}IO_3Si$: 489.1322].



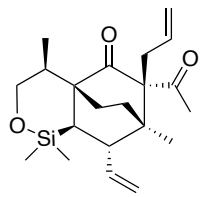

**Diketone (+)-3.4:** The following reaction was run in three batches, which were combined for purification.

Batch 1 (937 mg (–)-**3.5**, 1.92 mmol): To a cooled (–20 °C) solution of diisopropylamine (0.93 mL, 6.72 mmol) in THF (13.5 mL) was added *n*-BuLi (2.5 M/hexanes, 2.69 mL, 6.72 mmol) dropwise and the resulting solution was stirred at this temperature for 40 minutes. In a separate flask, iodide (–)-**3.5** (937 mg, 1.92 mmol) was dissolved in THF (13 mL) and cooled to –20 °C. The solution of LDA was added dropwise via cannula to the solution of (–)-**3.5** over 45 minutes while maintaining the temperature at –20 °C. The reaction mixture was allowed to warm to room temperature and quenched with saturated aqueous $NH_4Cl$ (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to provide the first batch of crude (+)-**3.4**.

Batch 2 (980 mg (–)-**3.5**, 2.01 mmol): The exact procedure as above with the same quantities of all reagents and solvents provided a second batch of crude (+)-**3.4**.

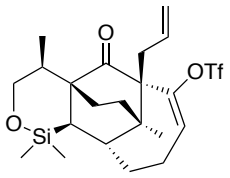
Batch 3 (1.03 g (–)-**3.5**, 2.11 mmol): Diisopropylamine (1.03 mL, 7.38 mmol) was dissolved in THF (14 mL) and cooled to –20 °C. A solution of *n*-BuLi (2.5 M/hexanes, 2.95 mL, 7.38 mmol) was added dropwise and the resulting solution was stirred at –20 °C for 40 minutes. In a separate flask, iodide (–)-**3.5** was dissolved in THF (14 mL) and cooled to –20 °C. The solution of LDA was transferred dropwise via cannula to the solution of (–)-**3.5** over 1 h while maintaining the temperature at –20 °C. The reaction

mixture was allowed to warm to room temperature and quenched with saturated aqueous $NH_4Cl$ (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The three crude batches were combined, adsorbed on silica, and purified by flash chromatography on silica gel (10:1 hexanes/EtOAc) to afford the title compound (1.68 g, 77%) as a white solid. X-ray quality crystals were obtained by slow evaporation from EtOAc. Melting point 123-125 °C. $[\alpha]_D^{20}$ +154 (*c* 0.91 $CHCl_3$). **IR** (neat) 2956, 2926, 2884, 2862, 1702, 1687, 1253, 1097, 1066 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.66 (dddd, *J* = 5.5, 8.3, 10.1, 16.8 Hz, 1 H), 4.96 (d, *J* = 10.1 Hz, 1 H), 4.90 (d, *J* = 17.0 Hz, 1 H), 3.77 - 3.62 (m, 2 H), 2.99 (dd, *J* = 5.5, 14.1 Hz, 1 H), 2.83 - 2.74 (m, 1 H), 2.51 - 2.37 (m, 2 H), 2.25 (dd, *J* = 8.2, 14.0 Hz, 1 H), 2.12 - 2.02 (m, 1 H), 1.98 - 1.90 (m, 1 H), 1.90 - 1.69 (m, 4 H), 1.53 - 1.42 (m, 2 H), 1.37 (td, *J* = 5.0, 13.5 Hz, 1 H), 1.18 (dd, *J* = 2.6, 5.9 Hz, 1 H), 0.88 (s, 3 H), 0.66 (d, *J* = 6.7 Hz, 3 H), 0.38 (s, 3 H), 0.13 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 211.2, 208.6, 135.6, 117.1, 70.8, 65.6, 49.3, 43.7, 43.5, 40.3, 36.0, 34.8, 33.5, 33.0, 30.0, 21.2, 18.8, 16.6, 12.1, 0.40, –1.73. **HRMS(ES+)** *m/z* 383.2021 [$(M+Na)^+$; calcd for $C_{21}H_{32}O_3SiNa$: 383.2018].



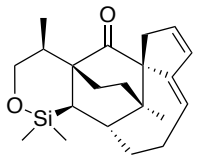

**Diene (–)-3.13:** To a cooled (–78 °C) solution of iodide (–)-**3.5** (10.4 mg, 0.0213 mmol) in THF (0.5 mL) was added NaHMDS (1 M/THF, 27 μL, 0.0277 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and saturated aqueous $NH_4Cl$ (0.5 mL) was added. Water (5 mL) and EtOAc (5 mL) were added and the layers were

separated. The aqueous layer was extracted with EtOAc (5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc) to afford the title compound (7.7 mg, 95%) as a colorless oil. $[\alpha]_D^{20}$ –23.2 (*c* 1.60 $CHCl_3$). **IR** (neat) 3076, 2956, 2924, 2880, 2857, 1699, 1636, 1471, 1420, 1383, 1353, 1253, 1105, 1065, 1000 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.82 (tdd, *J* = 7.3, 9.7, 16.8 Hz, 1 H), 5.37 (td, *J* = 9.6, 16.6 Hz, 1 H), 5.04 (dd, *J* = 0.8, 10.1 Hz, 1 H), 4.99 (dd, *J* = 1.7, 3.7 Hz, 1 H), 4.97 - 4.91 (m, 2 H), 3.67 - 3.56 (m, 2 H), 2.71 (dd, *J* = 7.7, 13.9 Hz, 1 H), 2.31 (ddd, *J* = 5.0, 6.5, 11.1 Hz, 1 H), 2.25 (dd, *J* = 6.5, 13.9 Hz, 1 H), 2.19 (s, 3 H), 2.08 (t, *J* = 9.4 Hz, 1 H), 2.03 - 1.95 (m, 2 H), 1.72 - 1.64 (m, 1 H), 1.30 (ddd, *J* = 7.3, 13.5, 15.5 Hz, 1 H), 1.06 (s, 3 H), 0.97 (dd, *J* = 2.1, 9.6 Hz, 1 H), 0.78 (d, *J* = 6.7 Hz, 3 H), 0.31 (s, 3 H), 0.08 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 210.4, 208.2, 139.3, 133.5, 118.5, 118.1, 67.1, 65.0, 51.2, 48.1, 41.9, 38.0, 35.4, 33.4, 32.4, 30.0, 21.4, 18.2, 12.7, 1.0, –1.9. **HRMS(ES+)** *m/z* 361.2199 [$(M+H)^+$; calcd for $C_{21}H_{33}O_3Si$: 361.2199].



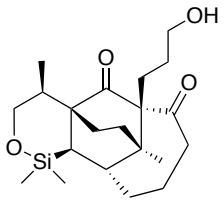

**Triflate (+)-3.19:** To a solution of ketone (+)-**3.4** (5 mg, 0.0138 mmol) and $PhN(Tf)_2$ (20 mg, 0.0552 mmol) in THF (0.3 mL) at –78 °C was added KHMDS (0.5 M/toluene, 36 μL, 0.0180 mmol) dropwise. After stirring for 0.5 h at this temperature, the reaction mixture was quenched by the rapid addition of pH 7 buffer (2 mL) at –78 °C and resulting mixture was allowed to warm temperature. Water (5 mL) and EtOAc (5 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc

(5 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (15:1 hexanes/EtOAc) to afford the title compound (6.7 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ +89.7 (*c* 0.75 $CHCl_3$). **IR** (neat) 2955, 2884, 2855, 1712, 1668, 1639, 1403, 1248, 1210, 1140 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.07 (dd, *J* = 3.8, 10.3 Hz, 1 H), 5.83 (dddd, *J* = 5.4, 7.9, 10.1, 16.9 Hz, 1 H), 5.03 (dd, *J* = 1.2, 10.3 Hz, 1 H), 4.99 (dd, *J* = 1.4, 16.8 Hz, 1 H), 3.75 - 3.63 (m, 2 H), 2.72 (dd, *J* = 5.4, 15.5 Hz, 1 H), 2.49 (dd, *J* = 7.8, 15.4 Hz, 1 H), 2.42 (ddd, *J* = 5.3, 6.5, 11.4 Hz, 1 H), 2.24 - 2.16 (m, 1 H), 2.10 - 2.00 (m, 3 H), 1.97 - 1.89 (m, 1 H), 1.84 (dddd, *J* = 2.6, 8.7, 11.3, 14.5 Hz, 1 H), 1.74 (ddd, *J* = 2.8, 4.6, 6.9 Hz, 1 H), 1.44 (ddd, *J* = 7.3, 10.7, 13.7 Hz, 1 H), 1.20 - 1.16 (m, 1 H), 1.15 (s, 3 H), 1.02 (dd, *J* = 2.4, 6.5 Hz, 1 H), 0.67 (d, *J* = 6.9 Hz, 3 H), 0.36 (s, 3 H), 0.11 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 208.8, 151.2, 134.9, 123.9, 117.9, 65.5, 62.3, 48.5, 44.1, 40.1, 36.4, 35.0, 33.5, 32.5, 27.7, 21.2, 18.5, 18.1, 12.2, 0.3, –2.0. **HRMS(ES+)** *m/z* 493.1685 [$(M+H)^+$; calcd for $C_{22}H_{32}F_3O_5SSi$: 493.1680].



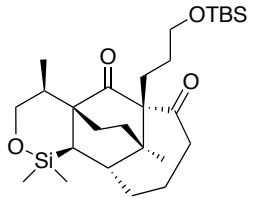

**Diene (+)-3.21:** A solution of triflate (+)-**3.19** (4 mg, 0.008 mmol), $(Bu_3Sn)_2$ (6 μL, 0.012 mmol), $Pd(PPh_3)_4$ (1 mg, 0.81 μmol) and thoroughly flame dried LiCl (1.7 mg, 0.041 mmol) in THF (0.2 mL) was heated to reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (15:1 hexanes/EtOAc) to afford the title compound (2 mg, 72%) as a colorless oil. $[\alpha]_D^{20}$ +56.7 (*c* 0.43 $CHCl_3$). **IR** (neat) 2953, 2920, 2852,

1700, 1684, 1684, 1644, 1435, 1379, 1209, 1144, 1095 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 3.5, 8.4 Hz, 1 H), 5.12 (br s, 1 H), 4.70 (br s, 1 H), 3.68 - 3.63 (m, 2 H), 2.59 (td, *J* = 2.5, 15.1 Hz, 1 H), 2.50 (td, *J* = 2.4, 14.9 Hz, 1 H), 2.34 - 2.27 (m, 2 H), 2.03 (td, *J* = 3.1, 14.4 Hz, 1 H), 1.97 (d, *J* = 10.3 Hz, 1 H), 1.96 - 1.93 (m, 1 H), 1.91 (ddd, *J* = 3.6, 7.7, 12.1 Hz, 1 H), 1.84 (ddd, *J* = 2.8, 5.0, 7.5 Hz, 1 H), 1.59 (ddd, *J* = 2.0, 3.6, 9.5 Hz, 1 H), 1.46 - 1.41 (m, 1 H), 1.29 - 1.22 (m, 2 H), 1.06 (s, 3 H), 1.03 (dd, *J* = 1.6, 7.3 Hz, 1 H), 0.76 (d, *J* = 6.7 Hz, 3 H), 0.34 (s, 3 H), 0.13 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 214.9, 144.4, 143.3, 119.2, 103.0, 65.4, 59.3, 47.1, 42.9, 36.8, 35.2, 34.0, 30.9, 28.7, 28.2, 21.0, 20.5, 18.4, 12.1, 0.2, –2.4. **HRMS(ES+)** *m/z* 343.2106 [$(M+H)^+$; calcd for $C_{21}H_{31}O_2Si$: 343.2093].



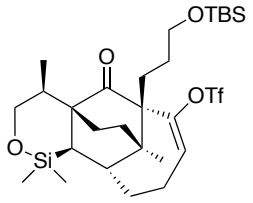

**Alcohol (+)-3.22:** The following reaction was run in two equal size batches side by side. A solution of 9-BBN (0.5M/THF, 0.48 mL, 0.237 mmol) was added to the alkene (+)-**3.4** (neat, 42.8 mg, 0.118 mmol) at room temperature and the reaction mixture was stirred for 1 h. The solution was cooled to 0 °C and a cold (0 °C) solution of aqueous NaOH (3.75 M, 0.31 mL, 1.18 mmol) was added dropwise. Then a cold (0 °C) solution of $H_2O_2$ (35 wt% in $H_2O$, 0.28 mL, 2.36 mmol) was carefully added dropwise. After stirring at 0 °C for 10 min, the cold bath was removed and the reaction mixture was vigorously stirred at room temperature for 1 h. The reaction mixture was diluted with water (10 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over $MgSO_4$ and

concentrated *in vacuo*. The combined residue from the two batches was purified by medium pressure liquid chromatography on silica gel (1:1 hexanes/EtOAc) to provide alcohol (+)-**3.22** (63.3 mg, 71%) as a colorless oil. $[\alpha]_D^{20}$ +173 (*c* 0.45 $CHCl_3$). **IR** (neat) 3421, 2954, 2916, 2874, 1697, 1457, 1253, 1063 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.78 - 3.66 (m, 2 H), 3.63 - 3.53 (m, 2 H), 2.84 - 2.77 (m, 1 H), 2.52 - 2.40 (m, 2 H), 2.28 (ddd, *J* = 4.2, 11.1, 13.7 Hz, 1 H), 2.07 (dd, *J* = 11.1, 14.1 Hz, 1 H), 1.96 - 1.85 (m, 2 H), 1.85 - 1.78 (m, 1 H), 1.78 - 1.71 (m, 1 H), 1.64 - 1.55 (m, 2 H), 1.53 - 1.41 (m, 3 H), 1.40 - 1.32 (m, 1 H), 1.26 (ddd, *J* = 5.4, 11.3, 18.2 Hz, 1 H), 1.20 (dd, *J* = 2.4, 5.7 Hz, 1 H), 0.84 (s, 3 H), 0.70 (d, *J* = 6.7 Hz, 3 H), 0.38 (s, 3 H), 0.14 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 212.8, 209.4, 70.2, 65.6, 63.1, 49.6, 43.5, 43.4, 40.4, 34.7, 33.6, 33.1, 29.8, 28.6, 26.5, 21.0, 19.0, 16.4, 12.2, 0.3, –1.7. **HRMS(ES+)** *m/z* 401.2124 [$(M+Na)^+$; calcd for $C_{21}H_{34}O_4SiNa$: 401.2124].



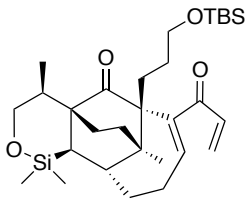

**Silyl ether (+)-3.23:** To a solution of alcohol (+)-**3.22** (401 mg, 1.06 mmol) and imidazole (216 mg, 3.18 mmol) in DMF (10 mL) was added TBSCl (207 mg, 1.38 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and allowed to warm to room temperature. The reaction mixture was quenched by the addition of water (10 mL) and diluted with EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica

gel (10:1 hexanes/EtOAc) to afford the title compound (490 mg, 94%) as a colorless oil. $[\alpha]_D^{20}$ +115 (*c* 0.57 $CHCl_3$). **IR** (neat) 2954, 2929, 2854, 1693, 1472, 1253, 1100 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.78 - 3.65 (m, 2 H), 3.61 (td, *J* = 5.2, 10.2 Hz, 1 H), 3.50 (ddd, *J* = 4.9, 8.6, 10.0 Hz, 1 H), 2.84 - 2.72 (m, 1 H), 2.50 - 2.44 (m, 1 H), 2.42 (dd, *J* = 6.7, 11.5 Hz, 1 H), 2.12 (dt, *J* = 4.4, 12.5 Hz, 1 H), 2.04 (dd, *J* = 10.9, 13.7 Hz, 1 H), 1.92 - 1.86 (m, 2 H), 1.85 - 1.78 (m, 1 H), 1.76 (td, *J* = 2.2, 14.5 Hz, 1 H), 1.74 - 1.69 (m, 1 H), 1.64 (dt, *J* = 4.4, 12.8 Hz, 1 H), 1.51 - 1.30 (m, 5 H), 1.22 - 1.14 (m, 1 H), 1.19 (dd, *J* = 2.2, 5.7 Hz, 1 H), 0.86 (s, 9 H), 0.82 (s, 3 H), 0.69 (d, *J* = 6.7 Hz, 3 H), 0.37 (s, 3 H), 0.12 (s, 3 H), 0.02 (s, 3 H), 0.00 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 212.8, 208.9, 70.1, 65.6, 63.4, 49.6, 43.6, 43.4, 40.4, 34.8, 33.6, 33.1, 29.8, 28.4, 27.0, 26.1, 21.0, 18.9, 18.4, 16.4, 12.3, 0.4, –1.7, –5.19, –5.15. **HRMS(ES+)** *m/z* 493.3167 [$(M+H)^+$; calcd for $C_{27}H_{49}O_4Si_2$: 493.3169].



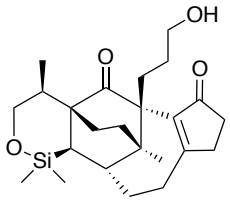

**Triflate (+)-3.24:** To a solution of ketone (+)-**3.23** (157.8 mg, 0.320 mmol) and $PhN(Tf)_2$ (171 mg, 0.480 mmol) in THF (3 mL) at –78 °C was added KHMDS (0.5 M/toluene, 1.80 mL, 0.898 mmol) dropwise. The reaction mixture was stirred for 0.5 h and quenched by the rapid addition of pH 7 buffer (2 mL) at –78 °C. The resulting mixture was allowed to warm to room temperature. Water (5 mL) and EtOAc (5 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic layers were washed with saturated aqueous $Na_2CO_3$ (3 mL), dried over

$MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (12:1 hexanes/EtOAc) to afford the title compound (171.3 mg, 86%) as a colorless oil. $[\alpha]_D^{20}$ +61.1 (*c* 1.20 $CHCl_3$). **IR** (neat) 2954, 2932, 2894, 2857, 1711, 1636, 1407, 1248, 1209, 1143, 1099 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.02 (dd, *J* = 3.9, 10.4 Hz, 1 H), 3.74 - 3.67 (m, 2 H), 3.63 (td, *J* = 4.7, 9.9 Hz, 1 H), 3.47 (dt, *J* = 4.6, 9.4 Hz, 1 H), 2.44 (ddd, *J* = 6.7, 12.5, 17.8 Hz, 1 H), 2.17 (tdd, *J* = 3.0, 13.7, 19.6 Hz, 1 H), 2.07 - 1.94 (m, 4 H), 1.93 - 1.85 (m, 1 H), 1.84 - 1.76 (m, 1 H), 1.75 - 1.71 (m, 1 H), 1.61 (ddd, *J* = 4.1, 8.8, 17.1 Hz, 1 H), 1.40 (ddd, *J* = 7.7, 10.7, 13.5 Hz, 1 H), 1.31 - 1.21 (m, 1 H), 1.18 - 1.14 (m, 2 H), 1.12 (s, 3 H), 1.00 (dd, *J* = 2.2, 6.3 Hz, 1 H), 0.86 (s, 9 H), 0.70 (d, *J* = 6.7 Hz, 3 H), 0.34 (s, 3 H), 0.09 (s, 3 H), 0.01 (s, 3 H), –0.01 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 209.6, 152.1, 123.8, 65.5, 62.9, 62.1, 48.9, 44.1, 40.4, 35.0, 34.0, 33.0, 29.4, 27.9, 26.0, 21.1, 18.4, 18.3, 18.0, 12.4, 0.2, –2.0, –5.32, –5.27. **HRMS(ES+)** *m/z* 625.2654 [$(M+H)^+$; calcd for $C_{28}H_{48}F_3O_6SSi_2$: 625.2662].

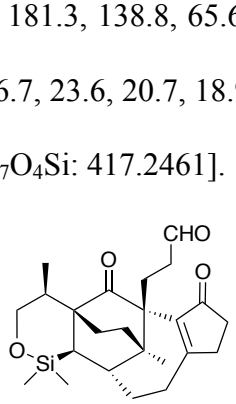



**Dienone (+)-3.25:** In a 10 mL pyrex reaction tube, LiCl (9.5 mg, 0.224 mmol) was thoroughly dried under vacuum using a heat gun, cooled under a stream of $N_2$, then $Pd(PPh_3)_4$ (3.2 mg, 0.0028 mmol) was added. A solution of triflate (+)-**3.24** (35.1 mg, 0.0.056 mmol) in DMF (2 mL + 1 mL rinse) was added to this mixture via cannula. The resulting light yellow solution was vigorously stirred and saturated with CO for 20 minutes, producing a deep yellow solution. Tetravinyltin (15 μL, 0.084 mmol) was

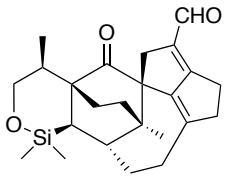
added, and the reaction tube was fitted with a CO balloon. The reaction mixture was heated to 90 °C for 10 minutes, and the precipitation of black Pd indicated completion of the reaction. After cooling to room temperature, the solution was diluted with EtOAc (5 mL) and washed with water (4 mL x 3). The combined aqueous layers were extracted with EtOAc (5 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography on silica gel (6:1 hexanes/EtOAc) to afford the title compound (21.4 mg, 72%) as a colorless oil. $[\alpha]_D^{20}$ +107 (*c* 0.66 $CHCl_3$). **IR** (neat) 2953, 2930, 2886, 2855, 1702, 1673, 1653, 1610, 1253, 1099, 1068 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 10.3, 17.4 Hz, 1 H), 6.38 - 6.33 (m, 2 H), 5.91 (dd, *J* = 1.6, 10.3 Hz, 1 H), 3.76 - 3.65 (m, 2 H), 3.44 (ddd, *J* = 4.8, 6.0, 10.3 Hz, 1 H), 3.30 (ddd, *J* = 5.5, 8.3, 9.9 Hz, 1 H), 2.46 (ddd, *J* = 5.4, 6.5, 11.5 Hz, 1 H), 2.43 - 2.37 (m, 1 H), 2.25 (ddd, *J* = 4.0, 11.9, 14.9 Hz, 1 H), 2.07 - 1.98 (m, 1 H), 1.97 - 1.93 (m, 2 H), 1.91 - 1.84 (m, 2 H), 1.76 - 1.66 (m, 3 H), 1.36 (ddd, *J* = 6.9, 11.1, 13.3 Hz, 1 H), 1.22 - 1.12 (m, 1 H), 1.09 (dd, *J* = 2.6, 5.7 Hz, 2 H), 1.05 (s, 3 H), 0.83 (s, 9 H), 0.69 (d, *J* = 6.7 Hz, 3 H), 0.35 (s, 3 H), 0.09 (s, 3 H), –0.03 (s, 3 H), –0.04 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 212.7, 196.4, 144.3, 140.3, 137.7, 131.5, 65.7, 63.1, 60.5, 49.6, 44.5, 40.6, 35.0, 33.8, 33.3, 28.2, 28.0, 26.1, 24.8, 22.0, 21.2, 19.2, 18.4, 12.5, 0.4, –1.8, –5.2. **HRMS(ES+)** *m/z* 553.3145 [$(M+Na)^+$; calcd for $C_{30}H_{50}O_4Si_2Na$: 553.3145].



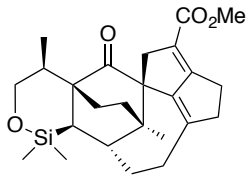
**Enone (+)-3.26:** To a solution of dienone (+)-**3.25** (21.4 mg, 0.040 mmol) in $CH_2Cl_2$ (3 mL) was added $SnCl_4$ (1 M/$CH_2Cl_2$, 60 μL, 0.060 mmol) dropwise at room temperature. The reaction mixture was stirred for 0.5 h and quenched with saturated aqueous $NH_4Cl$ (3 mL). The emulsion was vigorously stirred for 15 minutes and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (5 mL x 2) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2:1 EtOAc/hexanes) to afford the title compound (13.6 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ +119 (*c* 0.36 $CHCl_3$). **IR** (neat) 3439, 2954, 2922, 2878, 2856, 1695, 1618, 1443, 1378, 1280, 1253, 1129, 1099, 1065 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.77 - 3.65 (m, 3 H), 3.63 - 3.55 (m, 1 H), 3.12 (t, *J* = 12.1 Hz, 1 H), 2.72 (t, *J* = 14.5 Hz, 1 H), 2.61 (ddd, *J* = 1.6, 6.9, 19.0 Hz, 1 H), 2.55 (ddd, *J* = 3.4, 6.3, 19.2 Hz, 1 H), 2.50 - 2.46 (m, 1 H), 2.45 (ddd, *J* = 2.2, 3.2, 6.5 Hz, 1 H), 2.37 (ddd, *J* = 2.6, 6.5, 18.6 Hz, 1 H), 2.28 (br s, 1 H), 2.08 - 1.95 (m, 4 H), 1.94 - 1.85 (m, 2 H), 1.73 (dt, *J* = 2.8, 5.0 Hz, 1 H), 1.64 (dt, *J* = 5.5, 12.5 Hz, 1 H), 1.49 - 1.40 (m, 1 H), 1.34 (ddd, *J* = 7.6, 11.4, 13.9 Hz, 1 H), 1.20 (tdd, *J* = 5.2, 7.3, 12.1 Hz, 1 H), 1.06 (dd, *J* = 2.6, 5.7 Hz, 1 H), 0.85 (s, 3 H), 0.70 (d, *J* = 6.7 Hz, 3 H), 0.36 (s, 3 H), 0.11 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 211.9, 209.7, 181.3, 138.8, 65.6, 62.8, 59.3, 49.4, 44.0, 40.8, 36.2, 34.9, 34.3, 33.1, 31.8, 29.1, 27.8, 26.7, 23.6, 20.7, 18.9, 12.5, 0.4, –1.7. **HRMS(ES+)** *m/z* 417.2451 [$(M+H)^+$; calcd for $C_{24}H_{37}O_4Si$: 417.2461].



**Aldehyde (+)-3.27:** To a solution of alcohol (+)-**3.26** (8 mg, 0.019 mmol) in $CH_2Cl_2$ (2 mL) was added Dess-Martin periodinane (12 mg, 0.029 mmol) at room temperature. The reaction mixture was stirred for 0.5 h, then saturated aqueous $Na_2S_2O_3$ (1 mL) and saturated aqueous $NaHCO_3$ (1 mL) were added. The turbid mixture was vigorously stirred for 15 minutes and the resulting clear layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (5 mL x 2) and combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to afford the title compound (7.3 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$ +136 (*c* 0.24 $CHCl_3$). **IR** (neat) 2953, 2916, 2852, 2722, 1722, 1693, 1618, 1375, 1252, 1128, 1100, 1066 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 3.77 - 3.64 (m, 2 H), 3.20 (ddd, *J* = 5.2, 7.7, 13.5 Hz, 1 H), 2.70 (t, *J* = 14.5 Hz, 1 H), 2.61 (ddd, *J* = 1.6, 6.7, 18.8 Hz, 1 H), 2.55 (dd, *J* = 5.2, 9.1 Hz, 1 H), 2.52 (dd, *J* = 5.0, 8.7 Hz, 1 H), 2.45 (dddd, *J* = 1.0, 3.4, 7.7, 18.4 Hz, 1 H), 2.45 - 2.40 (m, 1 H), 2.37 (ddd, *J* = 2.6, 6.3, 18.4 Hz, 1 H), 2.17 (td, *J* = 6.8, 18.5 Hz, 1 H), 2.07 - 2.01 (m, 3 H), 1.98 (ddd, *J* = 2.2, 5.0, 15.5 Hz, 1 H), 1.88 (tt, *J* = 2.4, 14.2 Hz, 1 H), 1.74 (dt, *J* = 2.8, 5.4 Hz, 1 H), 1.41 - 1.32 (m, 1 H), 1.27 - 1.24 (m, 1 H), 1.24 - 1.16 (m, 1 H), 1.05 (dd, *J* = 1.4, 5.7 Hz, 1 H), 0.85 (s, 3 H), 0.64 (d, *J* = 6.7 Hz, 3 H), 0.37 (s, 3 H), 0.11 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 212.3, 208.8, 202.6, 180.7, 138.4, 65.7, 58.4, 49.4, 43.9, 41.0, 40.6, 36.0, 35.0, 34.0, 32.8, 31.6, 27.8, 26.5, 20.6, 19.1, 18.9, 12.3, 0.4, –1.7. **HRMS(ES+)** *m/z* 415.2306 [$(M+H)^+$; calcd for $C_{24}H_{35}O_4Si$: 415.2305].

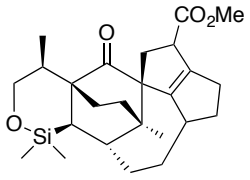


**Aldehyde (+)-3.28:** To a solution of aldehyde (+)-**3.27** (13.4 mg, 0.0323 mmol) in benzene (3 mL) was added $Bn_2NH_2O_2CCF_3$ (2 mg, 0.0065 mmol) at room temperature. The reaction mixture was heated to 60 °C for 14 h and allowed to cool to room temperature. The reaction mixture was diluted with pH 5 citrate buffer (3 mL) and extracted with $CH_2Cl_2$ (5 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (4:1 hexanes/EtOAc) to afford the title compound (7.7 mg, 60%) as a light yellow oil. $[\alpha]_D^{20}$ +74.9 (*c* 0.22 $CHCl_3$). **IR** (neat) 2915, 2873, 2848, 2798, 1706, 1638, 1607, 1440, 1381, 1346, 1253, 1226, 1101, 1064 $cm^{-1}$. **$^1$H NMR** (500 MHz, $C_6D_6$) δ 9.83 (s, 1 H), 3.66 (dd, *J* = 4.3, 11.8 Hz, 1 H), 3.57 (br s, 1 H), 3.46 (t, *J* = 11.7 Hz, 1 H), 3.13 - 3.02 (m, 2 H), 2.44 (dddd, *J* = 6.7, 11.1, 13.3, 18.0 Hz, 1 H), 2.39 - 2.24 (m, 2 H), 2.14 - 2.11 (m, 1 H), 2.07 - 1.98 (m, 1 H), 1.70 (dddd, *J* = 2.6, 4.2, 13.5, 15.5 Hz, 1 H), 1.64 - 1.57 (m, 1 H), 1.55 (ddd, *J* = 2.4, 5.5, 8.3 Hz, 1 H), 1.47 (td, *J* = 3.5, 17.7 Hz, 1 H), 1.35 - 1.29 (m, 2 H), 1.07 (dt, *J* = 3.3, 5.1 Hz, 1 H), 1.04 - 0.99 (m, 2 H), 0.67 (d, *J* = 6.7 Hz, 3 H), 0.63 (s, 3 H), 0.14 (s, 3 H), 0.08 (s, 3 H). **$^{13}$C NMR** (125 MHz, $C_6D_6$) δ 212.6, 185.8, 173.4, 154.9, 146.1, 129.6, 65.2, 57.1, 47.2, 42.9, 42.3, 42.0, 38.0, 35.7, 32.3, 28.4, 27.1, 23.0, 22.6, 20.7, 18.3, 12.5, 0.8, –2.4. **HRMS(ES+)** *m/z* 397.2199 [$(M+H)^+$; calcd for $C_{24}H_{33}O_3Si$: 397.2199].



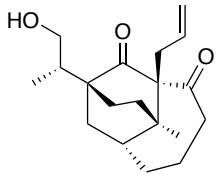

**Ester (+)-3.29:** To a solution of aldehyde (+)-**3.28** (7.7 mg, 0.0194 mmol) in MeOH (2 mL) was added NaCN (19 mg, 0.388 mmol) and AcOH (16 μL, 0.291 mmol)

sequentially at room temperature. The yellow reaction mixture was stirred for 0.5 h before $MnO_2$ (84 mg, 0.970 mmol) was added in one portion. The resulting dark reaction mixture was vigorously stirred for 12 h and filtered through a pad of celite, which was washed with $CH_2Cl_2$ (20 mL). The volatiles were removed *in vacuo* and the residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to afford the title compound (7 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$ +23.2 (*c* 0.13 $CHCl_3$). **IR** (neat) 2944, 2916, 2869, 2852, 1702, 1627, 1434, 1253, 1110, 1066 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.71 (s, 3 H), 3.68 - 3.61 (m, 2 H), 3.08 - 2.99 (m, 1 H), 2.87 - 2.84 (m, 3 H), 2.71 (m, 2 H), 2.46 - 2.37 (m, 1 H), 2.27 (ddd, *J* = 6.6, 12.8, 17.5 Hz, 1 H), 2.11 - 2.03 (m, 1 H), 2.03 - 1.95 (m, 2 H), 1.86 (ddd, *J* = 2.1, 5.9, 8.4 Hz, 1 H), 1.71 (d, *J* = 8.3 Hz, 2 H), 1.43 - 1.36 (m, 2 H), 1.08 (d, *J* = 8.3 Hz, 1 H), 0.89 (s, 3 H), 0.74 (d, *J* = 6.8 Hz, 3 H), 0.33 (s, 3 H), 0.15 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 214.5, 170.2, 166.6, 153.3, 145.2, 117.7, 65.3, 57.1, 51.2, 47.2, 43.8, 42.7, 42.2, 38.1, 35.3, 32.2, 28.2, 27.1, 25.5, 23.1, 21.0, 18.2, 12.3, 0.8, –2.2. **HRMS(ES+)** *m/z* 427.2303 [$(M+H)^+$; calcd for $C_{25}H_{35}O_4Si$: 427.2305].



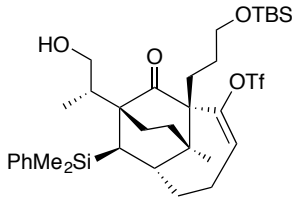

**Ester (+)-3.31:** To a solution of ester (+)-**3.29** (1.4 mg, 3.3 μmol) in $CH_2Cl_2$ (0.3 mL) was added $[(cod)(py)(PCy_3)]IrPF_6$ (2.6 mg, 3.3 μmol) and the reaction mixture was placed in a Parr bomb. The Parr bomb was pressured to 400 psi of $H_2$ and the reaction mixture was stirred at this pressure for 14 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (8:1 hexanes/EtOAc) to afford

the title compound (1.1 mg, 79%) as a colorless oil. $[\alpha]_D^{20}$ +10.3 (*c* 0.08 $CHCl_3$). **IR** (neat) 2922, 2857, 1736, 1703, 1638, 1461, 1440, 1251, 1163, 1100, 1070 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.73 (s, 3 H), 3.71 - 3.66 (m, 1 H), 3.66 - 3.57 (m, 2 H), 2.65 - 2.63 (m, 1 H), 2.62 (dd, *J* = 6.2, 13.5 Hz, 1 H), 2.50 (ddd, *J* = 2.8, 8.5, 12.0 Hz, 1 H), 2.43 (dd, *J* = 9.2, 13.7 Hz, 1 H), 2.40 - 2.35 (m, 1 H), 2.33 - 2.25 (m, 1 H), 2.19 (td, *J* = 5.6, 11.6 Hz, 1 H), 2.02 (dddd, *J* = 3.4, 7.3, 9.6, 14.7 Hz, 1 H), 1.95 (dd, *J* = 7.9, 12.0 Hz, 1 H), 1.90 (dd, *J* = 6.4, 8.8 Hz, 1 H), 1.83 - 1.76 (m, 1 H), 1.74 - 1.68 (m, 2 H), 1.67 - 1.63 (m, 1 H), 1.55 - 1.45 (m, 1 H), 1.35 (ddd, *J* = 7.9, 9.0, 15.6 Hz, 1 H), 1.02 (s, 3 H), 0.92 (m, 2 H), 0.80 (d, *J* = 6.6 Hz, 3 H), 0.33 (s, 3 H), 0.24 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 216.6, 174.8, 152.9, 146.8, 65.3, 63.4, 51.9, 48.3, 46.5, 42.0, 39.8, 39.7, 39.2, 36.8, 35.6, 33.3, 33.1, 32.5, 29.0, 28.1, 21.1, 18.7, 12.8, 1.9, –1.7. **HRMS(ES+)** *m/z* 429.2453 [$(M+H)^+$; calcd for $C_{25}H_{37}O_4Si$: 429.2461].



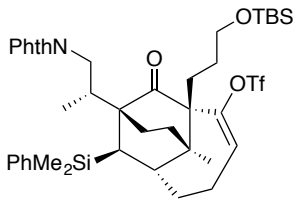

**Alcohol (+)-3.36:** To a solution of diketone (+)-**3.4** (19.5 mg, 0.054 mmol) in THF (1 mL) was added TBAF (1 M/THF, 0.11 mL, 0.108 mmol) at room temperature. The reaction mixture was stirred for 2 h and quenched by the addition of saturated aqueous $Na_2S_2O_3$ (1 mL). Water (5 mL) and EtOAc (5 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to afford the title compound (14.9 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$ +43.4 (*c* 0.50 $CHCl_3$). **IR** (neat) 3396,

3074, 2930, 2878, 1678, 1638, 1455, 1377, 1322, 1183, 1024 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.14 (dtd, *J* = 4.8, 9.7, 17.2 Hz, 1 H), 5.24 (td, *J* = 1.8, 17.2 Hz, 1 H), 5.07 (td, *J* = 1.4, 10.1 Hz, 1 H), 3.73 (dd, *J* = 6.3, 10.5 Hz, 1 H), 3.60 (dd, *J* = 7.3, 10.5 Hz, 1 H), 3.13 (ddd, *J* = 4.0, 10.3, 14.3 Hz, 1 H), 2.78 - 2.72 (m, 1 H), 2.56 (br s, 1 H), 2.37 (ddd, *J* = 3.8, 9.0, 14.4 Hz, 1 H), 2.16 (dd, *J* = 9.5, 13.1 Hz, 1 H), 2.02 - 1.94 (m, 2 H), 1.94 - 1.91 (m, 1 H), 1.91 - 1.87 (m, 1 H), 1.87 - 1.83 (m, 1 H), 1.82 - 1.71 (m, 3 H), 1.62 - 1.51 (m, 3 H), 1.21 (ddd, *J* = 4.8, 11.9, 13.9 Hz, 1 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 0.74 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 215.1, 139.3, 117.3, 70.5, 66.5, 65.8, 46.0, 45.8, 42.6, 37.8, 35.8, 34.9, 33.9, 30.8, 28.5, 20.0, 19.7, 17.3, 14.4. **HRMS(ES+)** *m/z* 305.2154 [$(M+H)^+$; calcd for $C_{19}H_{29}O_3$: 305.2038].



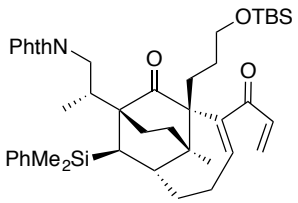

**Phenylsilane (+)-3.43:** To a solution of siloxane (+)-**3.24** (35 mg, 0.056 mmol) in $Et_2O$ (3 mL) was added PhLi (1.8 M/$Bu_2O$, 0.15 mL, 0.28 mmol) dropwise at room temperature. The reaction mixture was stirred for 15 minutes and quenched by the addition of saturated aqueous $NH_4Cl$ (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography on silica gel (5:1 hexanes/EtOAc) to afford the title compound (28 mg, 71%) as a colorless oil. $[\alpha]_D^{20}$ +87.7 (*c* 0.70 $CHCl_3$). **IR** (neat) 3407, 2953, 2932, 2890, 2857, 1711, 1642, 1405, 1248, 1212, 1143, 1108 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ

7.55 (dd, *J* = 1.6, 7.5 Hz, 2 H), 7.41 - 7.32 (m, 3 H), 5.99 (dd, *J* = 4.3, 10.2 Hz, 1 H), 3.72 - 3.65 (m, 2 H), 3.61 (td, *J* = 5.3, 10.1 Hz, 1 H), 3.45 (dt, *J* = 5.0, 9.3 Hz, 1 H), 2.13 - 2.05 (m, 1 H), 2.03 - 1.93 (m, 1 H), 1.93 - 1.82 (m, 2 H), 1.80 - 1.73 (m, 2 H), 1.73 - 1.68 (m, 3 H), 1.64 (dd, *J* = 11.2, 13.8 Hz, 1 H), 1.59 (dd, *J* = 3.0, 4.8 Hz, 1 H), 1.54 (ddd, *J* = 4.1, 8.7, 17.0 Hz, 1 H), 1.31 - 1.22 (m, 3 H), 1.24 (d, *J* = 7.1 Hz, 3 H), 1.05 (s, 3 H), 0.86 (s, 9 H), 0.54 (s, 3 H), 0.50 (s, 3 H), 0.01 (s, 6 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 213.7, 152.3, 138.4, 134.2, 129.6, 128.1, 123.8, 64.7, 63.0, 62.0, 50.6, 46.1, 42.9, 38.9, 33.4, 32.0, 29.0, 28.2, 28.1, 27.3, 26.1, 21.0, 18.4, 18.1, 14.0, –0.3, –1.3, –5.2, –5.3. **HRMS(ES+)** *m/z* 703.3141 [$(M+H)^+$; calcd for $C_{34}H_{54}F_3O_6SSi_2$: 703.3132].



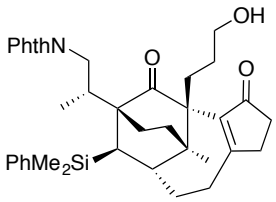

**Pthalimide (+)-3.44:** To a solution of alcohol (+)-**3.43** (18 mg, 0.025 mmol) in THF (3 mL) was added $PPh_3$ (14.6 mg, 0.056 mmol) and phthalimide (8.2 mg, 0.056 mmol). The resulting solution was cooled to 0 °C and DEAD (40 wt% in toluene, 21 μL, 0.070 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and the volatiles were removed *in vacuo*. The residue was purified by flash chromatography on silica gel (8:1 hexanes/EtOAc) to afford the title compound (17.5 mg, 84%) as a colorless oil. $[\alpha]_D^{20}$ +72.8 (*c* 0.52 $CHCl_3$). **IR** (neat) 2953, 2932, 2890, 2857, 1773, 1715, 1642, 1398, 1247, 1211, 1142 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 3.1, 5.4 Hz, 2 H), 7.73 (dd, *J* = 3.1, 5.4 Hz, 2 H), 7.58 - 7.52 (m, 2 H), 7.31 - 7.26 (m, 3 H), 6.01 (dd, *J* = 4.3, 10.2 Hz, 1 H), 3.96 (dd, *J* = 10.2, 13.2 Hz, 1 H), 3.68 - 3.59 (m, 1 H), 3.52

(dd, *J* = 2.1, 13.4 Hz, 1 H), 3.48 (dt, *J* = 5.0, 9.5 Hz, 1 H), 2.34 - 2.24 (m, 1 H), 2.03 - 1.88 (m, 4 H), 1.77 (d, *J* = 11.1 Hz, 4 H), 1.66 - 1.55 (m, *J* = 3.2 Hz, 3 H), 1.37 - 1.25 (m, 3 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 1.08 (s, 3 H), 0.83 (s, 9 H), 0.51 (s, 3 H), 0.46 (s, 3 H), 0.00 (s, 3 H), –0.02 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 212.0, 168.5, 152.3, 138.3, 134.3, 134.0, 132.3, 129.5, 127.9, 123.8, 123.3, 63.1, 61.7, 50.6, 46.0, 40.5, 39.8, 38.9, 33.3, 32.0, 29.1, 28.3, 28.2, 27.2, 26.0, 21.0, 18.4, 18.2, 14.3, –0.5, –1.4, –5.2, –5.3. **HRMS(ES+)** *m/z* 854.3161 [$(M+Na)^+$; calcd for $C_{42}H_{56}F_3NO_7SSi_2Na$: 854.3166].




**Dienone (+)-3.45:** In a 20 mL pyrex reaction tube, LiCl (3.3 mg, 0.079 mmol) was thoroughly dried under vacuum using a heat gun, cooled under a stream of $N_2$, then $Pd(PPh_3)_4$ (1.1 mg, 0.001 mmol) was added. A solution of triflate (+)-**3.44** (17 mg, 0.020 mmol) in DMF (2 mL + 1 mL rinse) was added to this mixture via cannula. The resulting light yellow solution was vigorously stirred and saturated aqueous with CO for 20 minutes, producing a deep yellow solution. Tetravinyltin (5 μL, 0.030 mmol) was added, and the reaction tube was fitted with a CO balloon. The reaction mixture was heated to 90 °C for 10 minutes, and the precipitation of black Pd indicated completion of the reaction. After cooling to room temperature, the solution was diluted with EtOAc (10 mL) and washed with water (4 mL x 3). The aqueous layer was extracted with EtOAc (10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography on silica gel (3:1 hexanes/EtOAc) to afford the product (8.9 mg, 61%) as

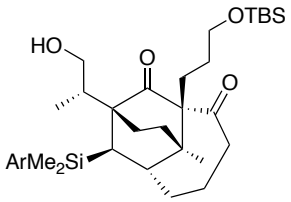
a colorless oil. $[\alpha]_D^{20}$ +110 (*c* 0.34 $CHCl_3$). **IR** (neat) 2953, 2932, 2885, 2857, 1772, 1714, 1671, 1648, 1613, 1398, 1255, 1098 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 3.1, 5.3 Hz, 2 H), 7.72 (dd, *J* = 3.0, 5.5 Hz, 2 H), 7.58 - 7.52 (m, 2 H), 7.35 - 7.28 (m, 3 H), 6.51 (dd, *J* = 10.4, 17.3 Hz, 1 H), 6.43 (dd, *J* = 4.4, 9.5 Hz, 1 H), 6.31 (dd, *J* = 1.4, 17.2 Hz, 1 H), 5.86 (dd, *J* = 1.2, 10.5 Hz, 1 H), 3.98 (dd, *J* = 9.9, 13.5 Hz, 1 H), 3.51 (d, *J* = 12.3 Hz, 1 H), 3.46 - 3.40 (m, *J* = 5.6, 10.4 Hz, 1 H), 3.37 - 3.28 (m, *J* = 6.3, 7.7 Hz, 1 H), 2.48 - 2.37 (m, 1 H), 2.30 - 2.20 (m, 2 H), 1.95 (dd, *J* = 4.4, 7.1 Hz, 1 H), 1.92 - 1.84 (m, 2 H), 1.80 (dd, *J* = 10.7, 13.9 Hz, 2 H), 1.72 - 1.57 (m, 4 H), 1.16 (d, *J* = 6.7 Hz, 3 H), 1.01 (s, 3 H), 0.98 - 0.95 (m, 1 H), 0.89 - 0.84 (m, 1 H), 0.80 (s, 9 H), 0.77 - 0.73 (m, 1 H), 0.51 (s, 3 H), 0.45 (s, 3 H), –0.05 (s, 3 H), –0.07 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 215.2, 195.5, 168.6, 145.1, 141.6, 138.7, 137.1, 134.3, 133.9, 132.3, 130.8, 129.3, 127.9, 123.3, 63.3, 60.2, 51.4, 46.3, 40.9, 39.9, 39.1, 32.8, 32.6, 29.0, 28.5, 27.8, 26.1, 25.5, 22.2, 21.3, 18.4, 14.5, –0.4, –1.4, –5.21, –5.19. **HRMS(ES+)** *m/z* 738.4011 $[(M+H)^+$; calcd for $C_{44}H_{60}NO_5Si_2$: 738.4010].




**Enone (+)-3.46:** To a solution of dienone (+)-**3.45** (5 mg, 0.007 mmol) in $CH_2Cl_2$ (1.5 mL) was added $SnCl_4$ (1 M/$CH_2Cl_2$, 33 μL, 0.033 mmol) dropwise at room temperature. The reaction mixture was stirred for 0.5 h and quenched with saturated aqueous $NH_4Cl$ (3 mL). The emulsion was vigorously stirred for 15 minutes and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (5 mL x 2) and the combined organic

layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2:1 EtOAc/hexanes) to afford the title compound (3.4 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ +78.3 (*c* 0.17 $CHCl_3$). **IR** (neat) 3420, 2949, 2928, 2873, 1768, 1713, 1650, 1620, 1399, 1377, 1356, 1322, 1111 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.72 (dd, *J* = 3.1, 5.4 Hz, 2 H), 7.58 - 7.51 (m, 2 H), 7.33 - 7.27 (m, 3 H), 3.87 (dd, *J* = 8.7, 13.7 Hz, 1 H), 3.72 - 3.66 (m, 1 H), 3.63 - 3.59 (m, 1 H), 3.62 (dd, *J* = 3.4, 13.5 Hz, 1 H), 3.09 (ddd, *J* = 2.4, 12.1, 14.1 Hz, 1 H), 2.53 (m, 2 H), 2.49 (dd, *J* = 3.0, 6.7 Hz, 1 H), 2.45 (dd, *J* = 3.1, 6.8 Hz, 1 H), 2.42 (dd, *J* = 2.3, 7.2 Hz, 1 H), 2.37 - 2.34 (m, 1 H), 2.34 - 2.29 (m, 1 H), 2.02 - 1.96 (m, 2 H), 1.92 (m, 2 H), 1.85 - 1.77 (m, 3 H), 1.69 - 1.59 (m, 3 H), 1.36 - 1.28 (m, 2 H), 1.21 (d, *J* = 6.9 Hz, 3 H), 0.80 (s, 3 H), 0.53 (s, 3 H), 0.46 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 214.9, 209.4, 181.7, 168.7, 139.3, 138.5, 134.3, 134.0, 132.3, 129.5, 128.0, 123.3, 62.9, 58.9, 51.2, 45.8, 41.2, 39.8, 39.2, 36.2, 33.0, 32.4, 31.3, 28.9, 28.3, 28.0, 26.5, 24.3, 20.7, 15.0, –0.3, –1.5. **HRMS(ES+)** *m/z* 624.3138 [$(M+H)^+$; calcd for $C_{38}H_{46}NO_5Si$: 624.3145].

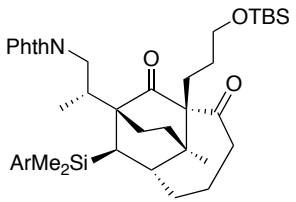
## 5-4: Experimental Procedures Relevant to Chapter 4




Ar = 4-MeOPh

**Alcohol (+)-4.3:** To a suspension of 4-iodoanisole (128 mg, 0.55 mmol) in $Et_2O$ (1.7 mL) at –78 °C was added *t*-BuLi (1.7M/pentane, 0.71 mL, 1.21 mmol) dropwise, at which point the suspension became a clear solution. The resulting solution was stirred at –78 °C for 20 min, then at room temperature for 45 min. In a separate flask, siloxane (+)-**3.23** (54.4 mg, 0.11 mmol) was dissolved in $Et_2O$ (1.1 mL), and the solution of 4-methoxyphenyllithium was added dropwise over 10 min via cannula, at room temperature. The reaction was quenched by addition of saturated aqueous $NH_4Cl$ (5 mL) and diluted with EtOAc (6 mL). The layers were separated and the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography on silica gel (4:1 hexanes/EtOAc) to afford the title compound (62.6 mg, 95%) as a colorless oil. $[\alpha]_D^{20}$ +92.0 (*c* 1.45 $CHCl_3$). **IR** (neat) 3442, 2954, 2931, 2895, 2860, 1696, 1594, 1503, 1461, 1277, 1250, 1183, 1108 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 3.82 (s, 3 H), 3.69 (dd, *J* = 6.1, 10.7 Hz, 1 H), 3.62 (dd, *J* = 2.8, 10.5 Hz, 1 H), 3.56 (td, *J* = 5.4, 10.4 Hz, 1 H), 3.45 (ddd, *J* = 5.2, 8.0, 10.0 Hz, 1 H), 2.66 (dd, *J* = 6.6, 17.5 Hz, 1 H), 2.36 (ddd, *J* = 7.4, 11.4, 17.6 Hz, 1 H), 2.10 (ddd, *J* = 4.3, 11.9, 13.4 Hz, 1 H), 2.06 - 1.97 (m, 1 H), 1.93 - 1.87 (m, 1 H), 1.87 - 1.82 (m, 1 H), 1.76 (t, *J* = 3.4 Hz, 2 H), 1.73 - 1.66 (m,

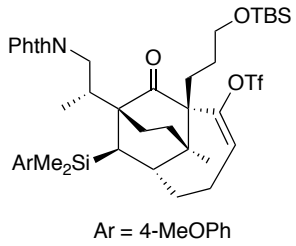
1 H), 1.66 - 1.55 (m, 2 H), 1.48 (ddd, *J* = 4.6, 11.8, 13.3 Hz, 1 H), 1.44 - 1.32 (m, 2 H), 1.29 (d, *J* = 6.9 Hz, 3 H), 1.27 - 1.11 (m, 3 H), 0.98 (td, *J* = 5.9, 13.9 Hz, 1 H), 0.86 (s, 9 H), 0.72 (s, 3 H), 0.52 (s, 3 H), 0.45 (s, 3 H), 0.01 (s, 3 H), 0.00 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 217.4, 209.3, 160.8, 135.6, 129.4, 113.8, 69.6, 64.5, 63.4, 55.2, 51.5, 45.0, 43.4, 42.4, 39.2, 32.2, 31.8, 29.7, 28.5, 28.0, 27.9, 26.1, 21.0, 18.4, 15.5, 13.7, –0.20, –0.98, –5.14, –5.18. **HRMS(ES+)** *m/z* 623.3539 [$(M+Na)^+$; calcd for $C_{34}H_{56}O_5Si_2Na$: 623.3533].



Ar = 4-MeOPh

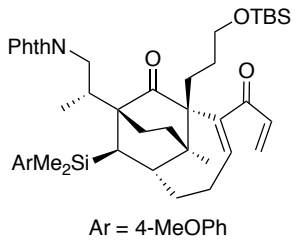
**Pthalimide (+)-4.4:** To a solution of alcohol (+)-**4.3** (120.5 mg, 0.20 mmol) in THF (6 mL) were added phthalimide (65 mg, 0.44 mmol) and $PPh_3$ (116 mg, 0.44 mmol). The solution was cooled to 0 °C and DEAD (40 wt%/toluene, 0.17 mL, 0.56 mmol) was added dropwise. The resulting solution was allowed to warm to room temperature and stir for 0.5 h. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography on silica gel (5:1 hexanes/EtOAc) to afford the title compound (144.7 mg, 99%) as a colorless oil. $[\alpha]_D^{20}$ +97.8 (*c* 1.24 $CHCl_3$). **IR** (neat) 2953, 2936, 2895, 2858, 1772, 1713, 1593, 1502, 1464, 1399, 1251, 1106 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.72 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.48 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 8.3 Hz, 2 H), 3.95 (dd, *J* = 10.1, 13.3 Hz, 1 H), 3.68 (s, 3 H), 3.57 (td, *J* = 5.3, 10.3 Hz, 1 H), 3.51 - 3.43 (m, 2 H), 2.71 (dd, *J* = 6.5, 17.2 Hz, 1 H), 2.38 (ddd, *J* = 7.5, 11.3, 18.4 Hz, 1 H), 2.29 - 2.19 (m, 1 H), 2.13 (ddd, *J* = 5.0, 11.3, 13.7 Hz,

1 H), 1.95 - 1.82 (m, 3 H), 1.82 - 1.70 (m, 2 H), 1.65 (dd, *J* = 10.9, 13.1 Hz, 1 H), 1.53 (ddd, *J* = 5.4, 11.0, 13.7 Hz, 1 H), 1.46 (t, *J* = 14.1 Hz, 1 H), 1.39 (td, *J* = 6.7, 14.5 Hz, 1 H), 1.34 - 1.21 (m, 3 H), 1.14 (d, *J* = 6.7 Hz, 3 H), 1.06 (td, *J* = 5.4, 12.9 Hz, 1 H), 0.82 (s, 9 H), 0.75 (s, 3 H), 0.47 (s, 3 H), 0.42 (s, 3 H), –0.01 (s, 3 H), –0.03 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 215.3, 209.4, 168.5, 160.6, 135.7, 133.9, 132.2, 129.3, 123.2, 113.6, 69.3, 63.4, 55.0, 51.3, 44.8, 43.3, 40.4, 39.4, 39.3, 32.2, 31.7, 29.8, 28.3, 27.9, 27.8, 26.0, 21.0, 18.4, 15.5, 14.1, –0.5, –1.1, –5.2. **HRMS(ES+)** *m/z* 730.3943 [$(M+H)^+$; calcd for $C_{42}H_{60}NO_6Si_2$: 730.3928].




**Triflate (+)-4.5:** To a solution of ketone (+)-**4.4** (61 mg, 0.084 mmol) and $PhN(Tf)_2$ (45 mg, 0.125 mmol) in THF (3 mL) at –78 °C was added KHMDS (0.5M/toluene, 0.33 mL, 0.167 mmol) dropwise. The light yellow solution was stirred at –78 °C for 0.5 h, quenched at this temperature by the dropwise addition of saturated aqueous $NH_4Cl$ (1.5 mL), then allowed to warm to room temperature. Water (5 mL) and EtOAc (10 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (10 mL x 2), and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography on silica gel (6:1 hexanes/EtOAc) to afford the title compound (52.8 mg, 73%) as a colorless oil. $[\alpha]_D^{20}$ +95.2 (*c* 0.56 $CHCl_3$). **IR** (neat) 2953, 2929, 2893, 2854, 1773, 1716, 1595, 1399, 1211 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.73 (dd, *J* = 3.2, 5.5

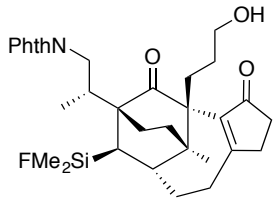
Hz, 2 H), 7.47 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 8.5, 2 H), 6.02 (dd, *J* = 4.3, 10.2 Hz, 1 H), 3.95 (dd, *J* = 10.3, 13.3 Hz, 1 H), 3.70 (s, 3 H), 3.63 (td, *J* = 5.3, 10.0 Hz, 1 H), 3.51 (dd, *J* = 2.2, 13.3 Hz, 1 H), 3.47 (ddd, *J* = 5.2, 8.7, 10.1 Hz, 1 H), 2.33 - 2.20 (m, 1 H), 2.05 - 1.72 (m, 8 H), 1.66 - 1.50 (m, 3 H), 1.38 - 1.19 (m, 3 H), 1.09 (d, *J* = 7.1, 3 H), 1.08 (s, 3 H), 0.83 (s, 9 H), 0.47 (s, 3 H), 0.43 (s, 3 H), 0.00 (s, 3 H), –0.02 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 212.1, 168.6, 160.7, 152.3, 135.8, 134.0, 132.2, 129.0, 123.8, 123.3, 113.7, 63.0, 61.7, 55.0, 50.6, 46.0, 40.5, 39.7, 38.9, 33.3, 32.1, 29.1, 28.4, 28.2, 27.1, 26.0, 21.0, 18.4, 18.2, 14.3, –0.51, –1.14, –5.26, –5.30. **HRMS(ES+)** *m/z* 884.3281 [$(M+Na)^+$; calcd for $C_{43}H_{58}F_3NO_8SSi_2Na$: 884.3272].



Ar = 4-MeOPh

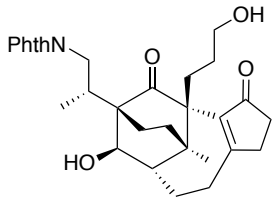
**Dienone (+)-4.6:** In a 20 mL pyrex reaction tube, LiCl (7.3 mg, 0.172 mmol) was thoroughly dried under vacuum using a heat gun, cooled under a stream of $N_2$, then $Pd(PPh_3)_4$ (2.5 mg, 0.0021 mmol) was added. A solution of triflate (+)-**4.5** (37 mg, 0.043 mmol) in DMF (2 mL + 2 mL rinse) was added to this mixture via cannula. The resulting light yellow solution was vigorously stirred and saturated aqueous with CO for 20 minutes, producing a deep yellow solution. Tetravinyltin (12 μL, 0.064 mmol) was added, and the reaction tube was fitted with a CO balloon. The reaction mixture was heated to 90 °C for 10 minutes, and the precipitation of black Pd indicated completion of the reaction. After cooling to room temperature, the solution was diluted with EtOAc (15 mL) and washed with water (4 mL x 3). The aqueous layer was extracted with EtOAc (10

mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography on silica gel (3:1 hexanes/EtOAc) to afford the product (32.1 mg, 97%) as a colorless oil. $[\alpha]_D^{20}$ +107 (*c* 0.97 $CHCl_3$). **IR** (neat) 2953, 2932, 2891, 2856, 1772, 1714, 1668, 1647, 1593, 1398, 1277, 1249, 1107 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 3.1, 5.4 Hz, 2 H), 7.71 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 6.51 (dd, *J* = 10.4, 17.3 Hz, 1 H), 6.44 (dd, *J* = 4.4, 9.5 Hz, 1 H), 6.30 (dd, *J* = 1.5, 17.3 Hz, 1 H), 5.86 (dd, *J* = 1.5, 10.4 Hz, 1 H), 4.02 - 3.94 (m, 1 H), 3.68 (s, 3 H), 3.50 (dd, *J* = 1.8, 13.5 Hz, 1 H), 3.42 (ddd, *J* = 4.9, 6.4, 10.5 Hz, 1 H), 3.31 (ddd, *J* = 6.1, 7.9, 9.9 Hz, 1 H), 2.40 (dddd, *J* = 3.0, 7.5, 10.5, 14.0 Hz, 1 H), 2.30 - 2.18 (m, 2 H), 1.97 - 1.73 (m, 6 H), 1.71 - 1.57 (m, 3 H), 1.31 - 1.18 (m, 2 H), 1.14 (d, *J* = 6.7 Hz, 3 H), 1.01 (s, 3 H), 0.99 - 0.90 (m, 1 H), 0.79 (s, 9 H), 0.46 (s, 3 H), 0.41 (s, 3 H), -0.05 (s, 3 H), –0.08 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 215.3, 195.5, 168.6, 160.6, 145.0, 141.7, 137.0, 135.8, 133.9, 132.3, 130.8, 129.4, 123.2, 113.6, 63.2, 60.2, 55.0, 51.4, 46.2, 40.9, 39.8, 39.1, 32.9, 32.5, 28.9, 28.5, 27.8, 26.0, 25.4, 22.2, 21.3, 18.4, 14.5, –0.4, –1.2, –5.24, –5.21. **HRMS(ES+)** *m/z* 768.4127 [$(M+H)^+$; calcd for $C_{45}H_{62}NO_6Si_2$: 768.4116].

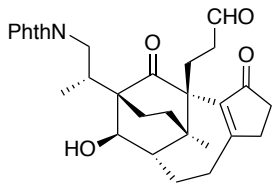



**Silyl fluoride (+)-3.47:** To a solution of enone (+)-**4.6** (32.1 mg, 0.042 mmol) in $CH_2Cl_2$ (3 mL) was added $HBF_4$•$OEt_2$ (57 μL, 0.42 mmol) dropwise at room temperature. The

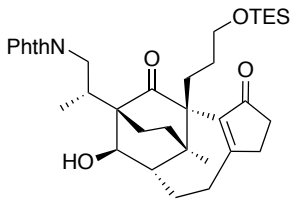
resulting solution was stirred for 0.5 h and quenched by the dropwise addition of saturated aqueous $NaHCO_3$ (2 mL). The reaction mixture was diluted with $CH_2Cl_2$ (8 mL) and water (3 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (10 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography (6:1 EtOAc/hexanes) to afford the title compound (19.5 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ +115 (*c* 0.54 $CHCl_3$). **IR** (neat) 3425, 2959, 2923, 2879, 1769, 1713, 1616, 1400 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 3.1, 5.4 Hz, 2 H), 7.70 (dd, *J* = 3.1, 5.4 Hz, 2 H), 3.94 (dd, *J* = 8.7, 13.7 Hz, 1 H), 3.68 (ddd, *J* = 5.5, 10.7, 16.1 Hz, 1 H), 3.65-3.61 (m, 1 H), 3.61 (dd, *J* = 3.0, 13.9 Hz, 1 H), 3.12 (dt, *J* = 2.0, 13.9 Hz, 1 H), 2.68 - 2.55 (m, 3 H), 2.50 (dddd, *J* = 3.6, 6.5, 9.7, 13.1 Hz, 1 H), 2.44 (dd, *J* = 3.2, 6.9 Hz, 1 H), 2.37 (ddd, *J* = 2.6, 6.3, 18.4 Hz, 1 H), 1.99-1.91 (m 5 H), 1.88-1.81 (m, 2 H), 1.69 (ddd, *J* = 6.1, 12.1, 13.7 Hz, 1 H), 1.56 - 1.38 (m, 3 H), 1.35-1.27 (m, 2 H), 1.29 (d, *J* = 6.9 Hz, 3 H), 0.88 (s, 3 H), 0.37 (d, *J* = 7.5 Hz, 3 H), 0.34 (d, *J* = 9 Hz, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 214.4, 209.3, 181.2, 168.7, 139.2, 134.0, 132.2, 123.3, 62.8, 59.1, 50.3, 44.4, 41.2, 40.3, 39.5, 36.2, 33.6 (d), 32.6, 31.4, 28.9, 28.4, 28.3, 26.4, 24.2, 20.7, 15.0, 0.78 (d), 0.06 (d). **HRMS(ES+)** *m/z* 548.2628 [$(M–OH)^+$; calcd for $C_{32}H_{39}FNO_4Si$: 548.2632].



**Diol (+)-3.48:** To a solution of silyl fluoride (+)-**3.47** (97 mg, 0.172 mmol) in DMF (6 mL) was added KF (99 mg, 1.71 mmol), followed by *m*-CPBA (75 wt%, 392 mg, 1.71 mmol). The reaction mixture was stirred at room temperature for 5 h, diluted with EtOAc (5 mL), and quenched by the addition of saturated aqueous $Na_2S_2O_3$ (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The suspension was vigorously stirred at room temperature for 15 minutes, diluted with water (5 mL) and EtOAc (15 mL), and the layers were separated. The organic layer was washed with brine (4 mL) and the combined aqueous layers were extracted with EtOAc (10 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography (EtOAc) to afford the title compound (64 mg, 74%) as a colorless oil. $[\alpha]_D^{20}$ +60.0 (*c* 0.46 $CHCl_3$). **IR** (neat) 3457, 2957, 2932, 2884, 1770, 1712, 1614, 1443, 1400, 1377, 1357, 1049 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 3.1, 5.4 Hz, 2 H), 7.70 (dd, *J* = 3.0, 5.5 Hz, 2 H), 4.03 (s, 1 H), 3.91 (d, *J* = 13.5 Hz, 1 H), 3.77 (dd, *J* = 9.2, 13.8 Hz, 1 H), 3.68 (ddd, *J* = 5.4, 10.7, 15.9 Hz, 1 H), 3.61 (qd, *J* = 4.3, 10.3 Hz, 1 H), 3.10 (dt, *J* = 2.5, 13.5 Hz, 1 H), 2.61 - 2.48 (m, 2 H), 2.44 (ddd, *J* = 3.4, 5.9, 18.4 Hz, 1 H), 2.37 (ddd, *J* = 2.8, 6.1, 12.7 Hz, 2 H), 2.40 - 2.28 (m, 1 H), 2.21 - 2.08 (m, 3 H), 2.07 - 1.97 (m, 2 H), 1.80 (td, *J* = 2.6, 14.1 Hz, 1 H), 1.76 - 1.68 (m, 2 H), 1.67 - 1.61 (m, 2 H), 1.61 - 1.54 (m, 1 H), 1.41 (s, 1 H), 1.31 - 1.20 (m, 1 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 0.85 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 214.8, 209.4, 181.1, 169.0, 139.1, 134.2, 132.1, 123.4, 62.8, 58.2, 55.4, 55.3, 41.0, 39.1, 37.3, 36.2, 32.2, 31.5, 28.9, 28.3, 25.1, 24.4, 20.3, 15.3. **HRMS(ES+)** *m/z* 528.2355 [$(M+Na)^+$; calcd for $C_{30}H_{35}NO_6Na$: 528.2362].

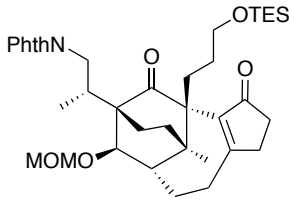



**Aldehyde (+)-4.7:** To a solution of diol (+)-**3.48** (3.2 mg, .0065 mmol) in $CH_2Cl_2$ (0.5 mL) was added $PhI(OAc)_2$ (2.7 mg, .0085 mmol) and TEMPO (one small crystal) sequentially at room temperature. The reaction mixture was stirred for 2 h, diluted with $CH_2Cl_2$ (3 mL), and quenched with saturated aqueous $Na_2S_2O_3$ (3 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (1:2 hexanes/EtOAc) to afford the title compound (3 mg, 92%) as a colorless oil. $[\alpha]_D^{20}$ +39.6 (*c* 0.33 $CHCl_3$). **IR** (neat) 3460, 2957, 2928, 2857, 2726, 1772, 1712, 1617, 1400, 1377, 1360, 1246, 1048 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 7.84 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.71 (dd, *J* = 3.1, 5.4 Hz, 2 H), 4.06 (d, *J* = 4.0 Hz, 1 H), 3.87 (d, *J* = 13.1 Hz, 1 H), 3.74 (dd, *J* = 9.8, 13.8 Hz, 1 H), 3.17 (ddd, *J* = 5.8, 7.7, 14.0 Hz, 1 H), 2.58 - 2.54 (m, 2 H), 2.52 (dd, *J* = 5.7, 7.9 Hz, 1 H), 2.45 (ddd, *J* = 3.4, 6.1, 18.6 Hz, 1 H), 2.38 (ddd, *J* = 2.8, 5.9, 18.4 Hz, 1 H), 2.34 - 2.24 (m, 3 H), 2.21 - 2.16 (m, 1 H), 2.16 - 2.09 (m, 2 H), 2.09 - 2.02 (m, 2 H), 1.81 (td, *J* = 2.2, 13.7 Hz, 1 H), 1.76 (br s, 1 H), 1.70 - 1.60 (m, 2 H), 1.28 - 1.23 (m, 1 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 0.87 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 215.3, 208.6, 202.5, 180.6, 169.1, 138.8, 134.2, 132.3, 123.5, 57.4, 55.3, 55.1, 40.9, 40.8, 38.9, 37.1, 36.1, 32.1, 31.4, 28.3, 25.3, 20.2, 19.9, 14.9. **HRMS(ES+)** *m/z* 526.2203 [$(M+Na)^+$; calcd for $C_{30}H_{33}NO_6Na$: 526.2206].



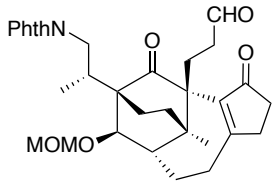

**Alcohol (+)-4.9:** To a cooled (0 °C) solution of diol (+)-**3.48** (46.9 mg, 0.092 mmol) in DMF (4 mL) was added imidazole (20 mg, 0.294 mmol) and TESCl (23 μL, 0.139 mmol) sequentially. After stirring at this temperature for 1.5 h, the reaction mixture was diluted with EtOAc (10 mL) and quenched with water (5 mL). The layers were separated and the organic layer was washed with brine (4 mL). The combined aqueous layers were extracted with EtOAc (10 mL x 2) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography (1:1 hexanes/EtOAc) to afford the product (46.9 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ +51.1 (*c* 0.64 $CHCl_3$). **IR** (neat) 3466, 2954, 2935, 2916, 2875, 1772, 1714, 1616, 1443, 1399, 1377, 1357, 1091 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 3.2, 5.4 Hz, 2 H), 7.71 (dd, *J* = 3.1, 5.4 Hz, 2 H), 4.00 (s, 1 H), 3.93 (d, *J* = 13.5 Hz, 1 H), 3.79 (dd, *J* = 9.7, 12.9 Hz, 1 H), 3.67 (ddd, *J* = 4.4, 6.9, 10.1 Hz, 1 H), 3.53 (ddd, *J* = 6.5, 8.1, 9.7 Hz, 1 H), 2.87 (ddd, *J* = 3.4, 11.9, 14.5 Hz, 2 H), 2.58 - 2.49 (m, 1 H), 2.49 - 2.40 (m, 1 H), 2.38 (td, *J* = 3.7, 7.1 Hz, 1 H), 2.34 (dd, *J* = 2.8, 5.9 Hz, 1 H), 2.30 (dd, *J* = 2.6, 6.1 Hz, 1 H), 2.20 - 2.10 (m, 2 H), 2.04 - 1.96 (m, 2 H), 1.81 - 1.70 (m, 3 H), 1.66 - 1.53 (m, 2 H), 1.35 - 1.26 (m, *J* = 5.2 Hz, 1 H), 1.26 - 1.16 (m, 1 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 0.91 (t, *J* = 7.9 Hz, 9 H), 0.84 (s, 3 H), 0.55 (q, *J* = 7.9 Hz, 6 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 214.4, 208.4, 179.1, 169.0, 139.2, 134.1, 132.2, 123.4, 63.1, 58.0, 55.6, 55.3,

41.0, 39.1, 37.3, 36.0, 32.2, 31.3, 29.1, 28.2, 25.2, 24.0, 20.4, 15.3, 6.9, 4.5. **HRMS(ES+)** *m/z* 642.3210 [$(M+Na)^+$; calcd for $C_{36}H_{49}NO_6SiNa$: 642.3227].



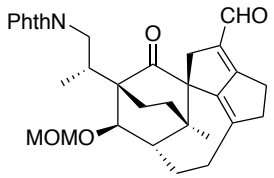

**Enone (+)-4.10:** To a solution of alcohol (+)-**4.9** (13.5 mg, 0.021 mmol) in 1,2-dichloroethane (1 mL) was added *i*-$Pr_2NEt$ (40 μL, 0.231), followed by MOMBr (17 μL, 0.210 mmol) at room temperature, and the reaction mixture was heated to 80 °C for 4 h. The red solution was cooled to room temperature, diluted with $CH_2Cl_2$ (1 mL), and quenched by the dropwise addition of pH 7 buffer (1 mL). The biphasic mixture was vigorously stirred for 15 minutes, diluted with additional $CH_2Cl_2$ (4 mL) and pH 7 buffer (3 mL), and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (8 mL x 2) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to afford the title compound (11.6 mg, 88%) as a colorless oil. $[\alpha]_D^{20}$ +53.2 (*c* 0.48 $CHCl_3$). **IR** (neat) 2953, 2935, 2911, 2880, 1774, 1715, 1618, 1398, 1095, 1028 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.70 (dd, *J* = 3.1, 5.4 Hz, 2 H), 4.74 (d, *J* = 6.9 Hz, 1 H), 4.66 (d, *J* = 7.1 Hz, 1 H), 3.97 (dd, *J* = 11.0, 13.0 Hz, 1 H), 3.92 (br s, 1 H), 3.54 (td, *J* = 7.3, 9.6 Hz, 1 H), 3.36 (s, 3 H), 2.90 (dt, *J* = 3.2, 13.0 Hz, 1 H), 2.59 - 2.45 (m, 2 H), 2.41 (ddd, *J* = 3.4, 6.7, 18.0 Hz, 1 H), 2.34 (dd, *J* = 2.1, 5.8 Hz, 1 H), 2.32 - 2.26 (m, 2 H), 2.24 - 2.11 (m, 3 H), 2.04 - 1.93 (m, 2 H), 1.85 (br. s., 1 H), 1.81 - 1.69 (m, 2 H), 1.68 - 1.63 (m, 1 H), 1.59 (td, *J* = 9.4, 13.4 Hz, 2 H), 1.38 - 1.23 (m, 2 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 0.90 (t, *J* = 8.0 Hz, 9 H), 0.86 (s, 3 H),

0.55 (q, *J* = 7.9 Hz, 6 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 214.5, 208.2, 179.2, 168.7, 139.4, 133.9, 132.3, 123.3, 96.0, 63.1, 58.1, 56.3, 54.4, 52.5, 40.8, 38.8, 36.8, 36.0, 32.3, 31.1, 29.1, 28.1, 25.9, 24.3, 20.3, 14.1, 6.9, 4.6. **HRMS(ES+)** *m/z* 664.3652 [$(M+H)^+$; calcd for $C_{38}H_{54}NO_7Si$: 664.3670].




**Aldehyde (+)-4.11:** To a solution of silyl ether (+)-**4.10** (7.4 mg, 0.011 mmol) in DMSO/THF (0.6 mL/0.3 mL) was added IBX (10.8 mg, 0.039 mmol) in one portion at room temperature. The reaction mixture was stirred vigorously for 12 h, diluted with EtOAc (10 mL) and washed with $H_2O$ (3 mL x 3). The aqueous layer was extracted with EtOAc (10 mL x 2) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to afford the title compound (5.7 mg, 95%) as a colorless oil. $[\alpha]_D^{20}$ +56.0 (*c* 0.39 $CHCl_3$). **IR** (neat) 2933, 2827, 2726, 1771, 1714, 1469, 1441, 1400, 1377, 1358, 1150, 1100, 1037 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 9.72 (d, *J* = 0.6 Hz, 1 H), 7.82 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.69 (dd, *J* = 3.0, 5.5 Hz, 2 H), 4.74 (d, *J* = 7.1 Hz, 1 H), 4.64 (d, *J* = 7.1 Hz, 1 H), 3.97 (s, 1 H), 3.83 (dd, *J* = 10.4, 13.6 Hz, 1 H), 3.66 (dd, *J* = 2.8, 13.7 Hz, 1 H), 3.36 (s, 3 H), 3.17 (td, *J* = 6.5, 13.5 Hz, 1 H), 2.61 - 2.51 (m, 3 H), 2.43 (dd, *J* = 3.7, 6.0 Hz, 1 H), 2.42 - 2.38 (m, 1 H), 2.36 (td, *J* = 3.2, 6.1 Hz, 1 H), 2.25 - 2.16 (m, 3 H), 2.16 - 2.10 (m, 1 H), 2.07 - 1.98 (m, 2 H), 1.90 - 1.85 (m, 1 H), 1.78 (tt, *J* = 2.4, 14.2 Hz, 1 H), 1.71 - 1.64 (m, 1 H), 1.64 - 1.57 (m, 2 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 0.87 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 215.5, 208.4, 202.5, 180.5, 168.8, 139.0,

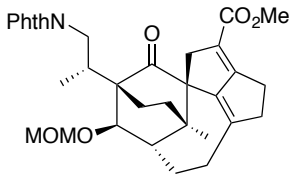
133.9, 132.3, 123.3, 95.9, 78.3, 57.4, 56.3, 54.5, 52.2, 40.9, 40.5, 38.6, 36.4, 36.1, 32.1, 31.1, 28.2, 26.0, 21.8, 20.2, 20.1, 13.8. **HRMS(ES+)** *m/z* 570.2472 [$(M+Na)^+$; calcd for $C_{32}H_{37}NO_7Na$: 570.2468].




**Aldehyde (+)-4.12:** To a solution of aldehyde (+)-**4.11** (10 mg, 0.018 mmol) in benzene (3.5 mL) was added a solution of dibenzylammonium trifluoroacetate (7.1 mg, 0.023 mmol) in $CH_2Cl_2$ (0.3 mL) at room temperature. The reaction mixture was heated to 50 °C for 17 h. The resulting bright yellow solution was cooled to room temperature, diluted with pH 5.0 citrate buffer (5 mL), and extracted with $CH_2Cl_2$ (10 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative TLC (silica, 1:1 hexanes/EtOAc) to afford the product (5.3 mg) as a light yellow oil, along with recovered starting material (3 mg).

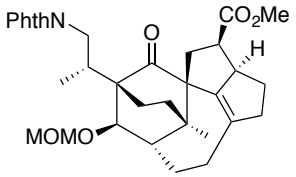
The recovered starting material (3 mg, 0.0055 mmol) was dissolved in PhH (1.5 mL) and a solution of dibenzylammonium trifluoroacetate (2.2 mg, 0.0071 μmol) in $CH_2Cl_2$ (0.2 mL) was added. The reaction mixture was heated to 50 °C for 21 hours. An identical workup and purification procedure provided a second batch of product (1.3 mg; total 6.6 mg, 69%). $[\alpha]_D^{20}$ +44.6 (*c* 0.15 $CHCl_3$). **IR** (neat) 2925, 2851, 1771, 1714, 1662, 1637, 1608, 1464, 1442, 1399, 1378, 1351, 1037 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 9.70 (s, 1 H), 7.82 (dd, *J* = 3.2, 5.4 Hz, 2 H), 7.69 (dd, *J* = 3.0, 5.4 Hz, 2 H), 4.79 (d, *J* = 7.1 Hz, 1 H), 4.66 (d, *J* = 7.1 Hz, 1 H), 4.06 (dd, *J* = 9.7, 13.5 Hz, 1 H), 4.06 (br. s., 1 H), 3.62 (dd, *J* = 3.1, 13.6 Hz, 1 H), 3.38 (s, 3 H), 3.07 - 2.92 (m, 3 H), 2.81 - 2.75 (m, 1 H), 2.41 -

2.31 (m, 1 H), 2.28 (ddd, *J* = 3.3, 11.3, 14.0 Hz, 1 H), 2.17 (d, *J* = 3.6 Hz, 1 H), 2.14 (s, 1 H), 2.11 - 2.02 (m, 1 H), 2.02 - 1.98 (m, 1 H), 1.98 - 1.88 (m, 2 H), 1.74 (ddd, *J* = 3.0, 11.5, 14.3 Hz, 1 H), 1.59 (ddd, *J* = 6.1, 11.5, 13.3 Hz, 1 H), 1.55 (s, 3 H), 1.11 (d, *J* = 6.9 Hz, 2 H), 0.90 (s, 3 H). **$^{13}$C NMR** (125 MHz, $C_6D_6$) δ 214.5, 185.4, 172.0, 168.2, 153.7, 146.7, 133.1, 132.5, 129.7, 122.7, 95.7, 74.5, 57.3, 55.6, 53.2, 51.4, 43.2, 41.4, 40.3, 37.0, 35.6, 31.8, 25.9, 24.2, 22.4, 21.9, 20.2, 13.5. **HRMS(ES+)** *m/z* 530.2548 [$(M+H)^+$; calcd for $C_{32}H_{36}NO_6$: 530.2543].



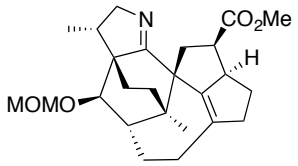

**Ester (+)-4.14:** To a solution of aldehyde (+)-**4.12** (6.6 mg, 12 μmol) in MeOH (1.0 mL) were added NaCN (11.8 mg, 0.24 mmol) and AcOH (10 μL, 0.18 mmol) sequentially. The yellow reaction mixture was stirred for 0.5 h before $MnO_2$ (73 mg, 0.84 mmol) was added in one portion. The resulting dark reaction mixture was vigorously stirred for 12 hours and filtered through a pad of celite, which was washed with $CH_2Cl_2$ (20 mL). After removal of the solvent *in vacuo*, the residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to afford the title compound (5.5 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ +29.1 (*c* 0.15 $CHCl_3$). **IR** (neat) 2926, 2850, 1772, 1714, 1664, 1628, 1465, 1438, 1398, 1379, 1352, 1109, 1037 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 3.1, 5.4 Hz, 2 H), 7.69 (dd, *J* = 3.1, 5.4 Hz, 2 H), 4.78 (d, *J* = 7.1 Hz, 1 H), 4.65 (d, *J* = 7.1 Hz, 1 H), 4.08 (dd, *J* = 9.4, 13.7 Hz, 1 H), 4.06 (br. s., 1 H), 3.70 (s, 3 H), 3.61 (dd, *J* = 3.0, 13.7 Hz, 1 H), 3.37 (s, 3 H), 3.09 - 2.93 (m, 2 H), 2.83 (m, 2 H), 2.68 (d, *J* = 3.2 Hz, 2 H), 2.36 - 2.27 (m, 1 H), 2.26 (ddd, *J* = 3.2, 11.2, 14.0 Hz, 1 H), 2.20 - 2.11 (m, 1

H), 2.11 - 2.00 (m, 2 H), 1.99 - 1.84 (m, 3 H), 1.73 (ddd, *J* = 3.4, 11.8, 15.0 Hz, 1 H), 1.61 - 1.53 (m, 1 H), 1.10 (d, *J* = 7.1 Hz, 3 H), 0.91 (s, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 216.2, 169.0, 168.6, 166.3, 152.2, 146.0, 133.8, 132.2, 123.1, 118.1, 96.0, 74.4, 57.5, 56.2, 53.4, 51.4, 51.1, 45.1, 41.8, 40.4, 37.2, 35.4, 31.9, 26.0, 25.5, 24.4, 22.0, 20.7, 13.4. **HRMS(ES+)** *m/z* 560.2651 [$(M+H)^+$; calcd for $C_{33}H_{38}NO_7$: 560.2648].




**Ester (–)-4.15:** To a solution of unsaturated ester (+)-**4.14** (5.8 mg, 0.010 mmol) in 1,2-dichloroethane (0.6 mL) was added [(cod)(py)($PCy_3$)]IrBArF (15 mg, 0.010 mmol). The reaction mixture was placed in a Parr bomb and the bomb was pressurized to 900 psi of $H_2$. The reaction mixture was vigorously stirred at this pressure for 19 h. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography on silica gel (4:1 hexanes/EtOAc) to afford the title compound (4.7 mg, 84%, 4:1 d.r.) as a colorless oil. The diastereomers were inseparable by flash chromatography but an analytically pure sample of the major diastereomer could be obtained by careful purification utilizing medium pressure liquid chromatography (4:1 hexanes/EtOAc). $[\alpha]_D^{20}$ –64.5 (*c* 0.27 $CHCl_3$). **IR** (neat) 2946, 2878, 2852, 1772, 1714, 1646, 1437, 1399, 1355, 1320, 1167, 1097, 1039 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.69 (dd, *J* = 3.0, 5.5 Hz, 2 H), 4.85 (s, 2 H), 4.14 (d, *J* = 4.6 Hz, 1 H), 3.85 (dd, *J* = 7.1, 13.9 Hz, 1 H), 3.78 (dd, *J* = 6.5, 13.9 Hz, 1 H), 3.60 (s, 3 H), 3.42 (s, 3 H), 3.06 - 2.98 (m, 1 H), 2.93 (ddd, *J* = 4.5, 9.1, 10.6 Hz, 1 H), 2.61 (dd, *J* = 7.1, 14.3 Hz, 1 H), 2.55 - 2.45 (m, 1 H), 2.38 (dd, *J* = 4.6, 13.7 Hz, 1 H), 2.35 - 2.24 (m, 3 H), 2.19 - 2.09

(m, 3 H), 2.09 - 2.01 (m, 1 H), 1.90 (dt, *J* = 1.8, 6.3 Hz, 1 H), 1.67 - 1.57 (m, 3 H), 1.51 - 1.42 (m, 2 H), 1.08 (s, 3 H), 1.06 (d, *J* = 7.3 Hz, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 215.3, 176.3, 168.7, 139.3, 135.5, 133.9, 132.4, 123.2, 97.0, 75.2, 61.4, 56.4, 54.8, 52.9, 51.3, 49.8, 43.0, 42.5, 41.3, 38.6, 38.0, 34.1, 33.4, 27.5, 25.8, 24.0, 23.2, 22.5, 14.4. **HRMS(ES+)** *m/z* 584.2618 [$(M+Na)^+$; calcd for $C_{33}H_{39}NO_7Na$: 584.2624].

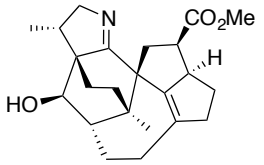



**Imine (–)-4.16:** To a solution of phthalimide (–)-**4.15** (4.7 mg, 0.0083 mmol) in absolute EtOH (1 mL) was added hydrazine hydrate (13 μL, 0.415 mmol) and the reaction mixture was stirred at room temperature for 12 h. The volatiles were removed *in vacuo* and the residue was redissolved in EtOH (2 mL). Saturated aqueous $NH_4Cl$ (0.1 mL) was added and the resulting suspension was stirred at room temperature for 0.5 h. The reaction mixture was heated to 70 °C for 18 h, at which point LCMS analysis indicated complete consumption of the starting material. The reaction mixture was cooled to room temperature and partitioned between saturated aqueous $Na_2CO_3$ (5 mL) and $CH_2Cl_2$ (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative TLC (1:1 hexanes/EtOAc) to afford the title compound (2.5 mg, 73% over 2 steps) as a colorless oil. $[\alpha]_D^{20}$ –101 (*c* 0.17 $CHCl_3$). **IR** (neat) 2947, 2928, 2865, 1733, 1644, 1436, 1371, 1318, 1192, 1167, 1099, 1048, 1019 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.80 (d, *J* = 6.7 Hz, 1 H), 4.71 (d, *J* = 6.7 Hz, 1 H), 3.94 (dd, *J* = 7.1, 15.3 Hz, 1 H), 3.83 (d, *J* = 4.6 Hz, 1 H), 3.64 (s, 3 H), 3.62 - 3.56 (m, 1 H), 3.44 (dd, *J* = 1.8, 15.3

Hz, 1 H), 3.41 (s, 3 H), 3.16 (dt, *J* = 4.8, 9.9 Hz, 1 H), 2.58 (dd, *J* = 5.0, 13.5 Hz, 1 H), 2.55 - 2.47 (m, 1 H), 2.35 (dd, *J* = 9.1, 13.5 Hz, 1 H), 2.32 - 2.27 (m, 1 H), 2.21 - 2.11 (m, 3 H), 2.05 (ddd, *J* = 1.8, 6.3, 8.5 Hz, 1 H), 2.02 - 1.96 (m, 1 H), 1.87 (td, *J* = 7.1, 11.9 Hz, 1 H), 1.80 (app t, *J* = 5.4 Hz, 1 H), 1.47 (ddd, *J* = 6.9, 11.3, 13.4 Hz, 1 H), 1.34 (ddd, *J* = 2.6, 11.1, 13.5 Hz, 1 H), 1.29 - 1.21 (m, 3 H), 1.10 (s, 3 H), 0.93 (d, *J* = 7.1 Hz, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 185.4, 176.3, 141.7, 132.5, 96.6, 75.3, 67.7, 56.3, 56.0, 54.5, 52.5, 51.1, 49.8, 42.6, 42.3, 39.7, 39.1, 37.4, 34.5, 27.5, 25.6, 24.4, 23.9, 22.1, 16.3. **HRMS(ES+)** *m/z* 414.2644 [$(M+H)^+$; calcd for $C_{25}H_{36}NO_4$: 414.2644].

## $Ph_2BBr$

**Bromodiphenylborane:** The following procedure was slightly modified from a known protocol.[1] A 20 mL sealed tube was charged with $PhSiMe_3$ (4.1 mL, 24.0 mmol) and cooled to 0 °C. Boron tribromide (1.2 mL, 12.0 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature. The reaction mixture was heated to 180 °C for 18 h. The resulting black reaction mixture was cooled to room temperature and transferred to a 25 mL round bottomed flask via cannula. Trimethylsilyl bromide was distilled (bp 79 °C/760 torr) off, followed by a small amount of unreacted $PhSiMe_3$ (bp 60 °C/0.1 torr). The remaining residue was distilled (bp 120-122 °C/0.1 torr) to afford $Ph_2BBr$ (2.67 g, 91%) as a colorless liquid which rapidly becomes a yellow and eventually red liquid upon storage. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 1.3, 8.0 Hz, 2 H), 7.62 (tt, *J* = 1.2, 7.3 Hz, 1 H), 7.50 (t, *J* = 7.7 Hz, 2 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 137.6, 133.2, 128.0.




**(–)-Calyciphylline N (1.15):** To a solution of imine (–)-**4.16** (2.5 mg, 0.006 mmol) in $CH_2Cl_2$ (1 mL) was added a freshly prepared solution of $Ph_2BBr$ (1 M/$CH_2Cl_2$, 30 μL, 0.030 mmol) at –40 °C. The resulting light yellow solution was allowed to warm to room temperature and stirred for an additional 0.5 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL) and the emulsion was vigorously stirred at room temperature for 10 minutes. The reaction mixture was diluted with $CH_2Cl_2$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (8 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative TLC (100% EtOAc) to afford (–)-calyciphylline N (1.7 mg, 79%) as a colorless oil. $[\alpha]_D^{20}$ –85.3 (*c* 0.11 $CHCl_3$). **IR** (neat) 3358, 2923, 2859, 1733, 1667, 1642, 1554, 1461, 1436, 1373, 1318, 1192, 1168 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$)[2] δ 4.01 - 3.99 (m, 1 H), 3.93, (dd, *J* = 7.0, 15.4 Hz, 1 H), 3.59 (s, 3 H), 3.56 - 3.52 (m, 1 H), 3.43 (dd, *J* = 1.2, 15.5 Hz, 1 H), 3.13 (ddd, *J* = 5.3, 9.3, 10.7 Hz, 1 H), 2.51 (dd, *J* = 5.2, 13.5 Hz, 1 H), 2.47 - 2.42 (m, 1 H), 2.30 (dd, *J* = 9.2, 13.6 Hz, 1 H), 2.25 (dd, *J* = 9.1, 15.5 Hz, 1 H), 2.19 - 2.09 (m, 3 H), 2.05 - 2.00 (m, 2 H), 1.89 - 1.85 (m, 1 H), 1.82 (dt, *J* = 7.3, 12.1 Hz, 1 H), 1.57 - 1.54 (m, 1 H), 1.42 - 1.38 (m, 1 H), 1.26 (ddd, *J* = 2.2, 11.1, 13.3 Hz, 1 H), 1.21 (m, 1 H), 1.19 - 1.15 (m, 1 H), 1.04 (s, 3 H), 0.97 (d, *J* = 7.1 Hz, 3 H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 185.3, 176.2, 141.4, 132.1, 68.0, 57.0, 54.4, 52.6, 51.9, 51.1, 42.7, 42.3, 39.5, 38.8, 37.0,

34.6, 27.4, 25.3, 23.4, 22.7, 21.5, 16.7. **HRMS(ES+)** *m/z* 370.2381 [$(M+H)^+$; calcd for $C_{23}H_{32}NO_3$: 370.2382].

## 5-5: References

1. Haubold, W.; Herdtle, J; Gollinger, W; Einholz, W. *J. Organomet. Chem.* **1986**, *315*, 1-8.

2. This $^1H$ NMR spectrum was referenced to $CDCl_3$ at δ 7.21.

# Appendix 1: Spectra Relevant to Chapter 2

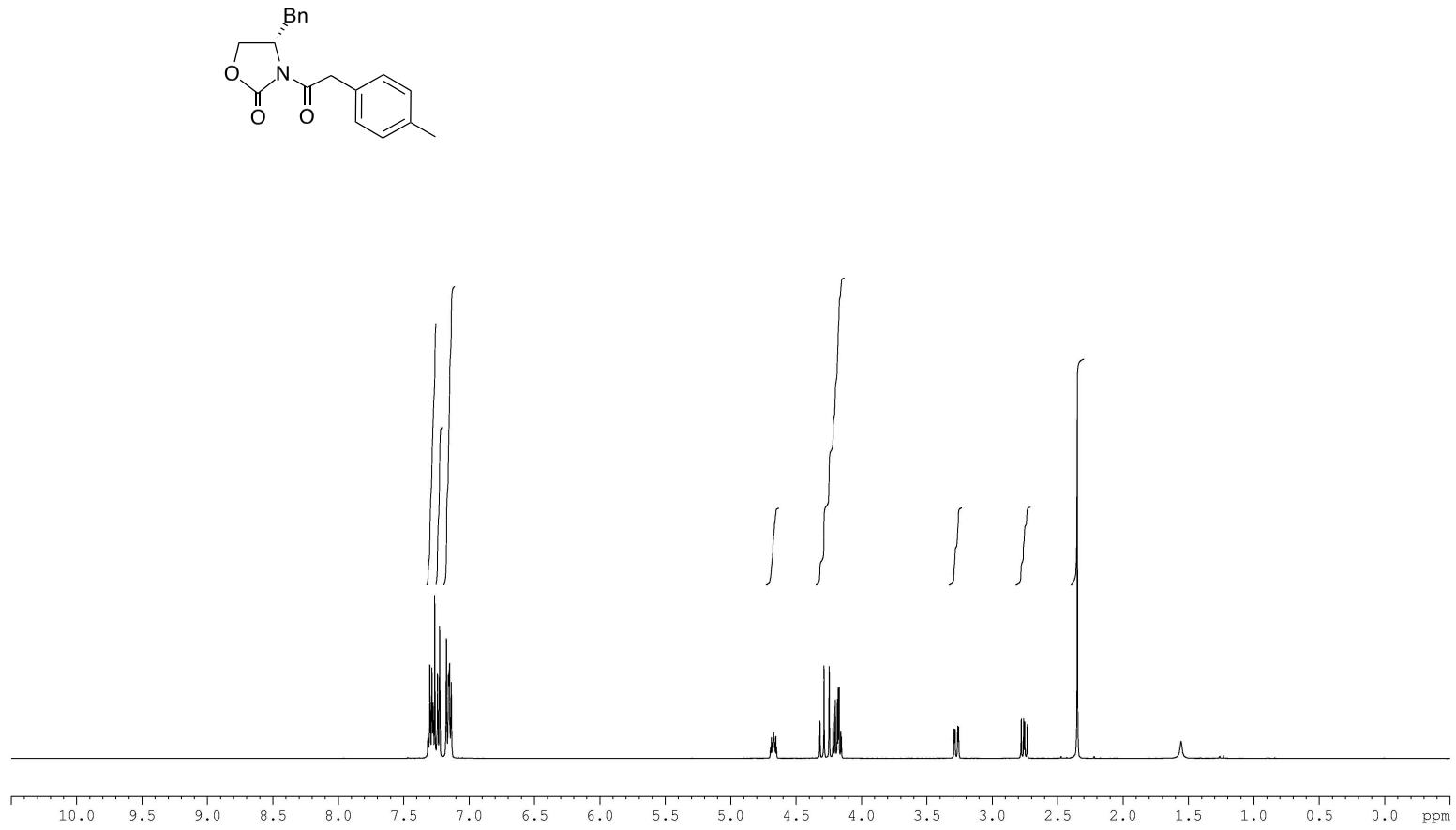



**Figure A1-1:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**2.10** in $CDCl_3$

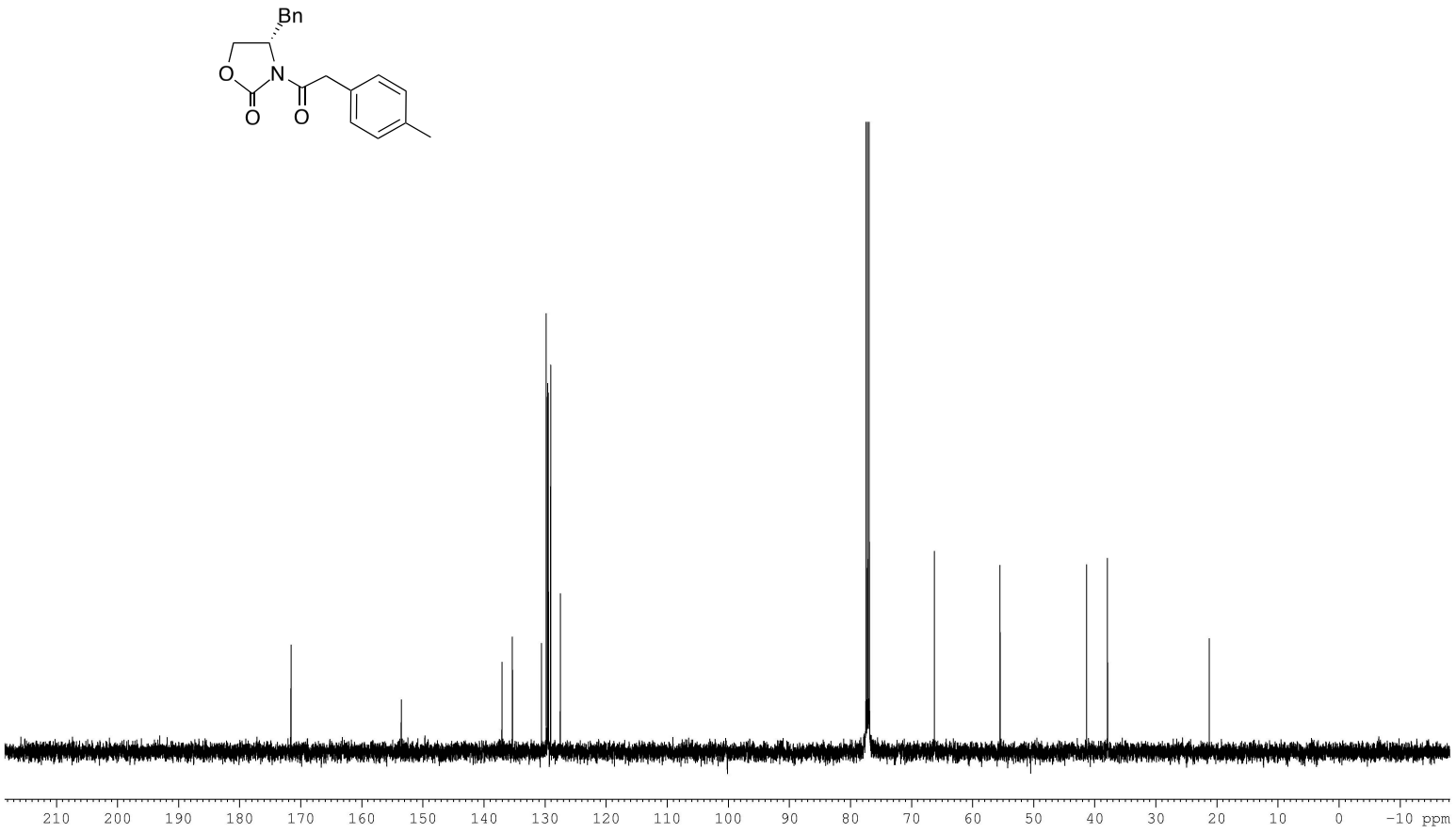



**Figure A1-2:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**2.10** in $CDCl_3$

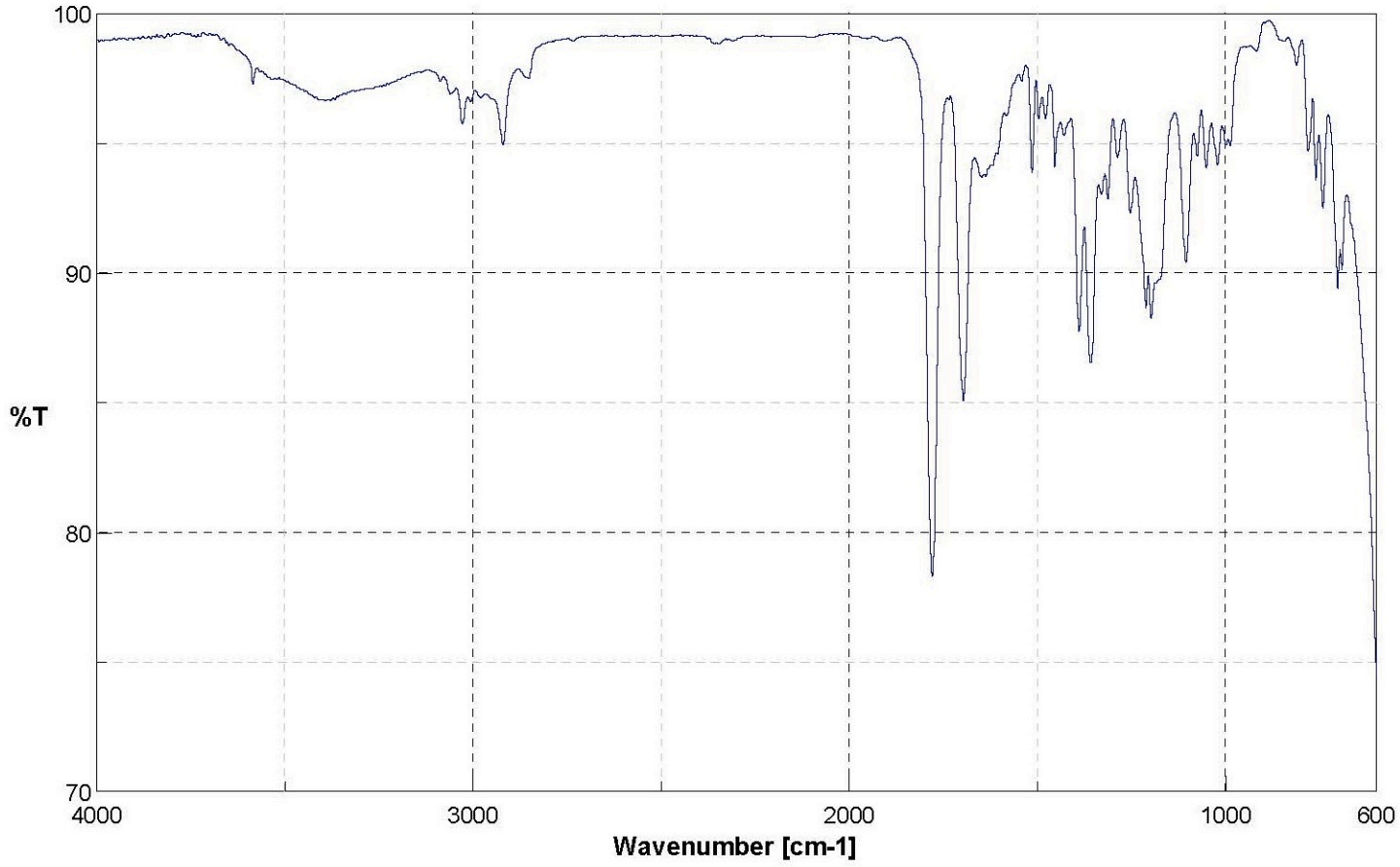



**Figure A1-3:** The Infrared Spectrum of Compound (+)-**2.10**

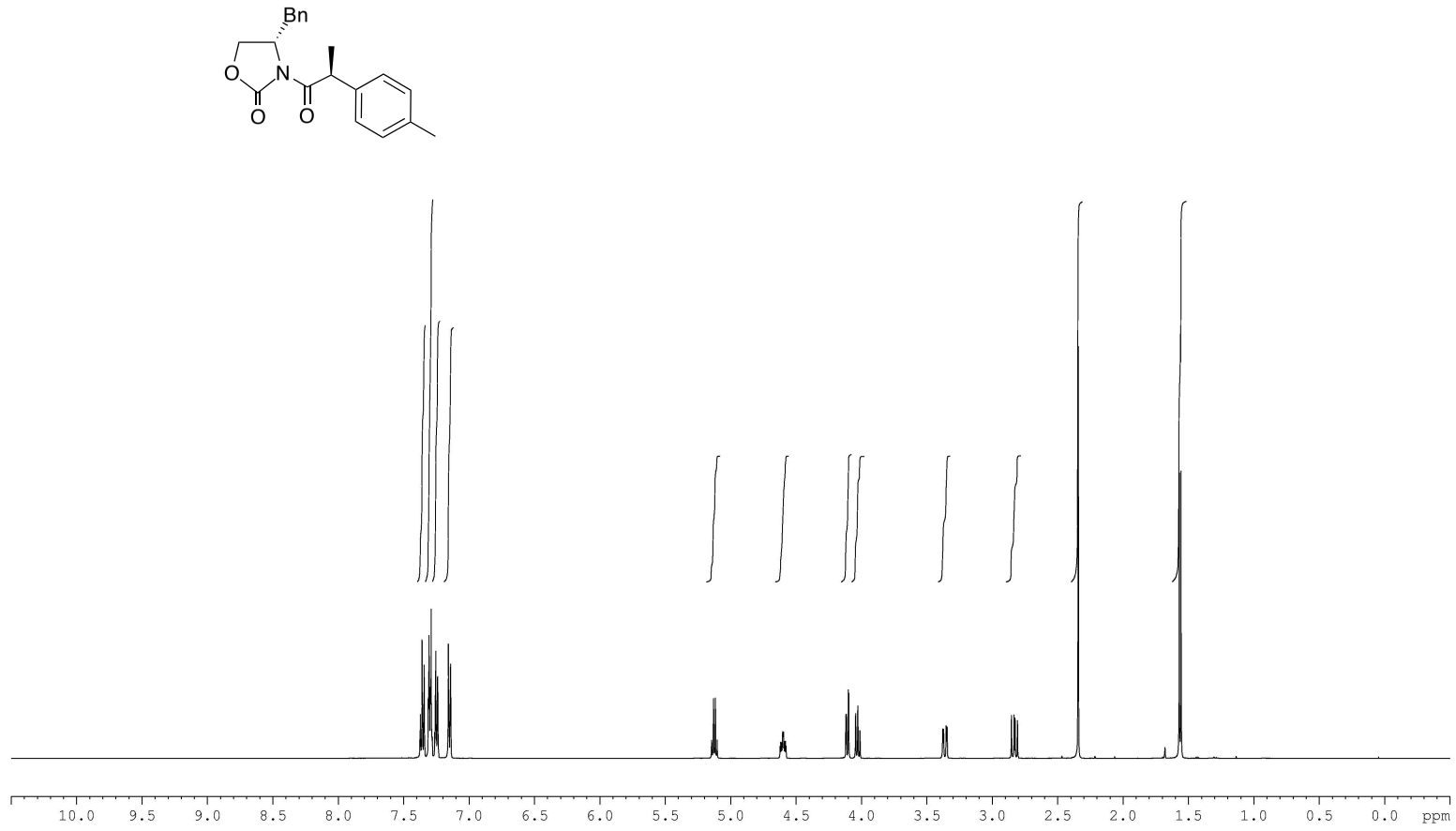



**Figure A1-4:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**2.11** in $CDCl_3$

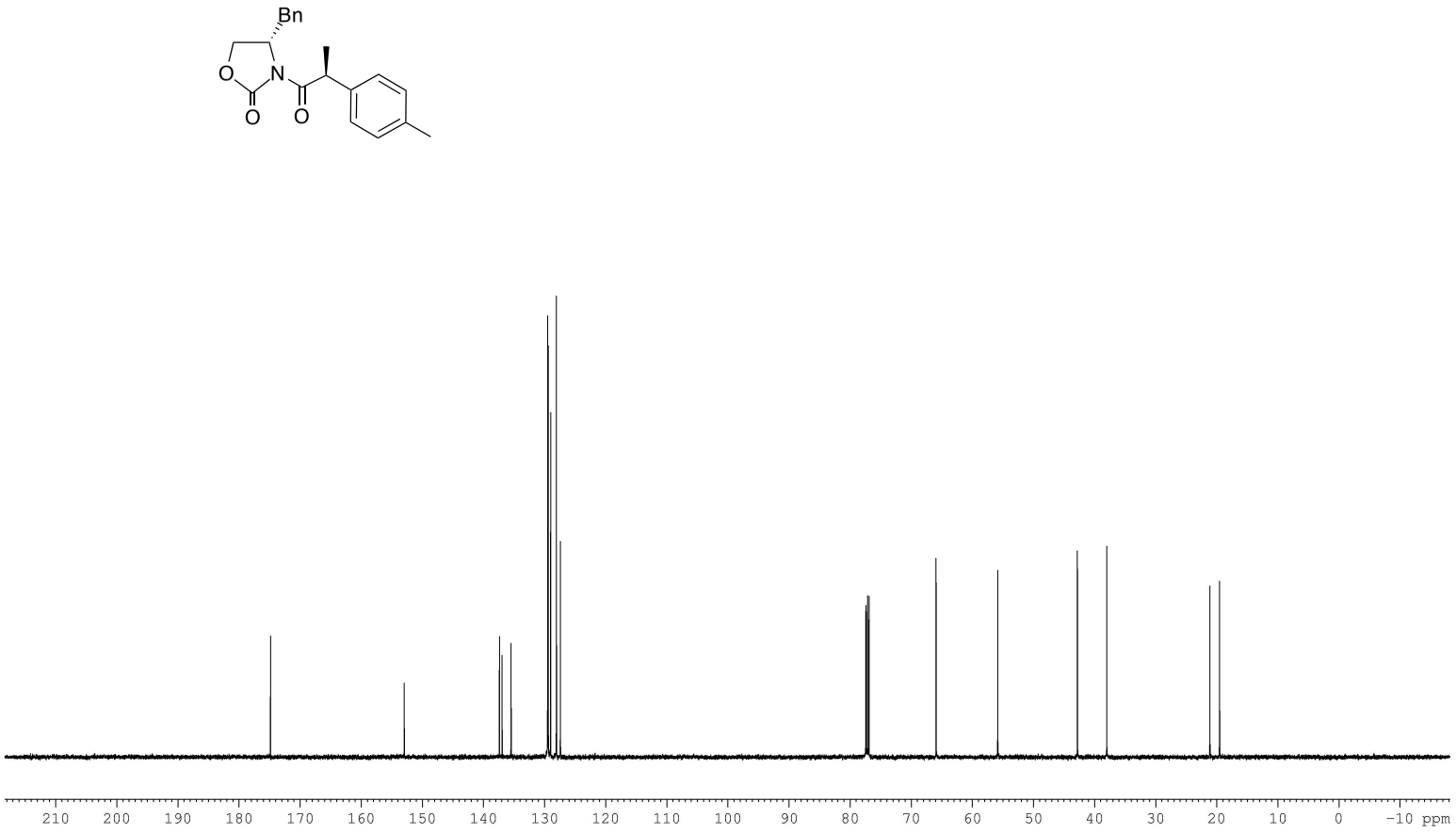



**Figure A1-5:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**2.11** in $CDCl_3$

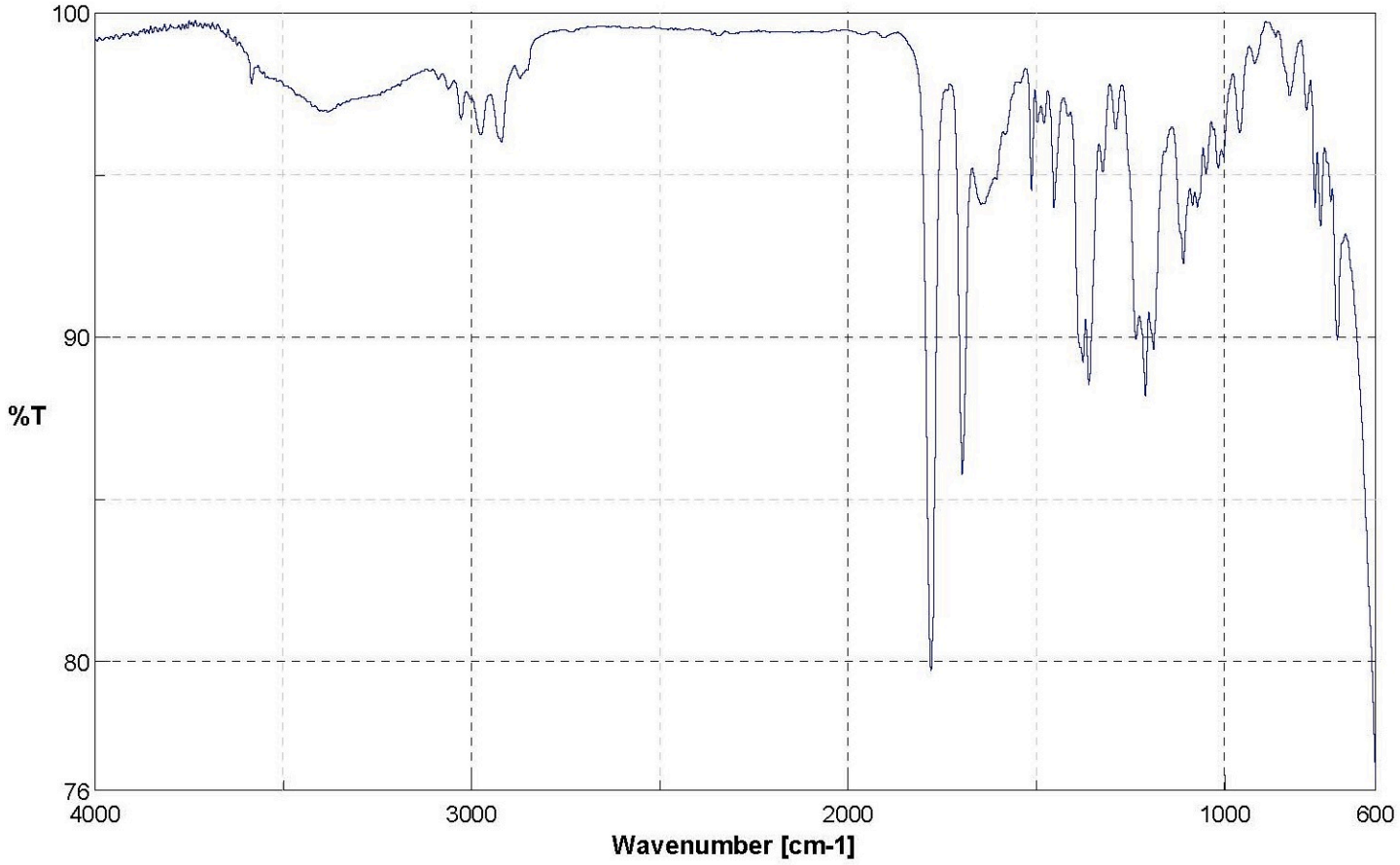



**Figure A1-6:** The Infrared Spectrum of Compound (+)-**2.11**

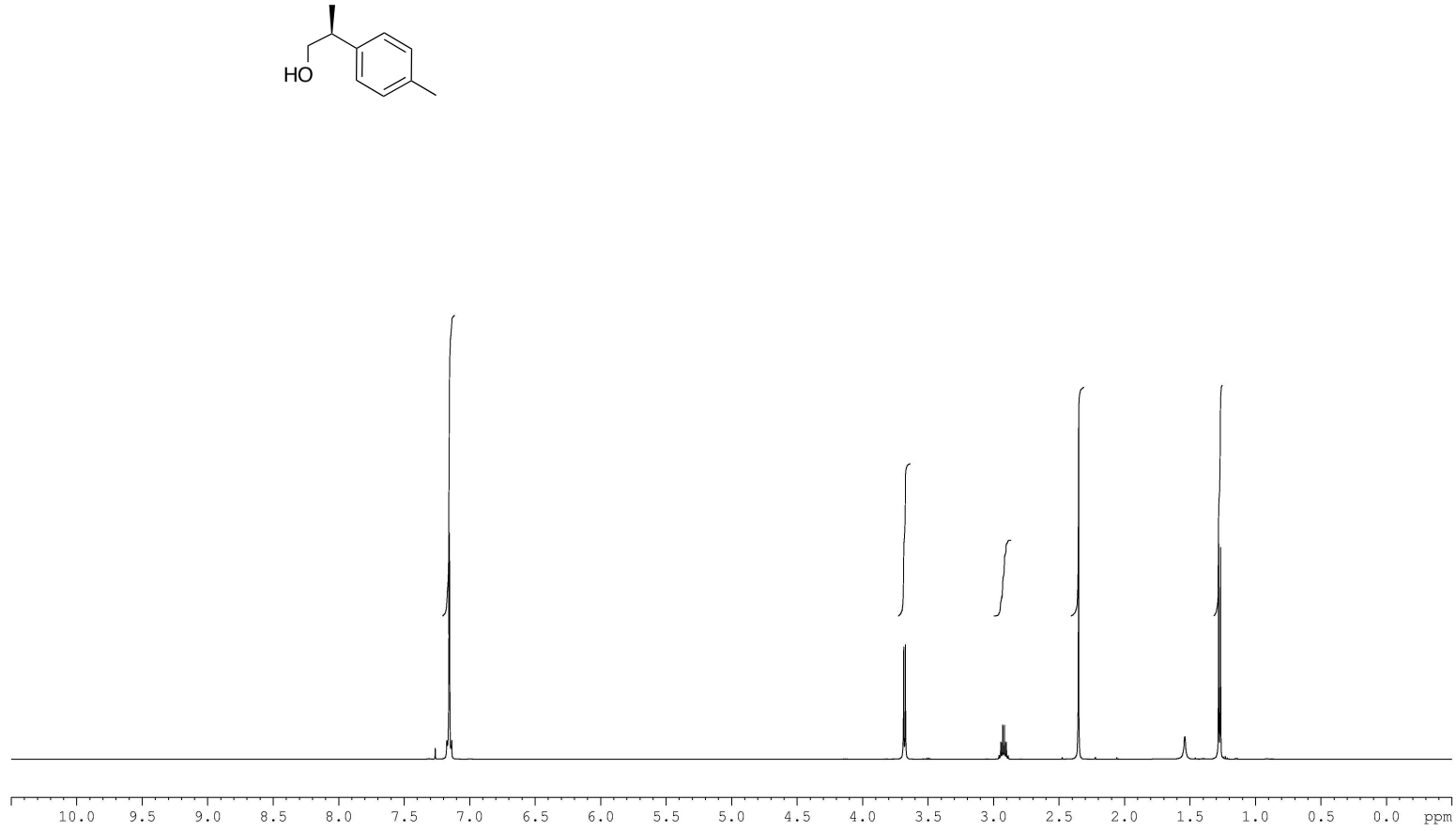



**Figure A1-7:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.12** in $CDCl_3$

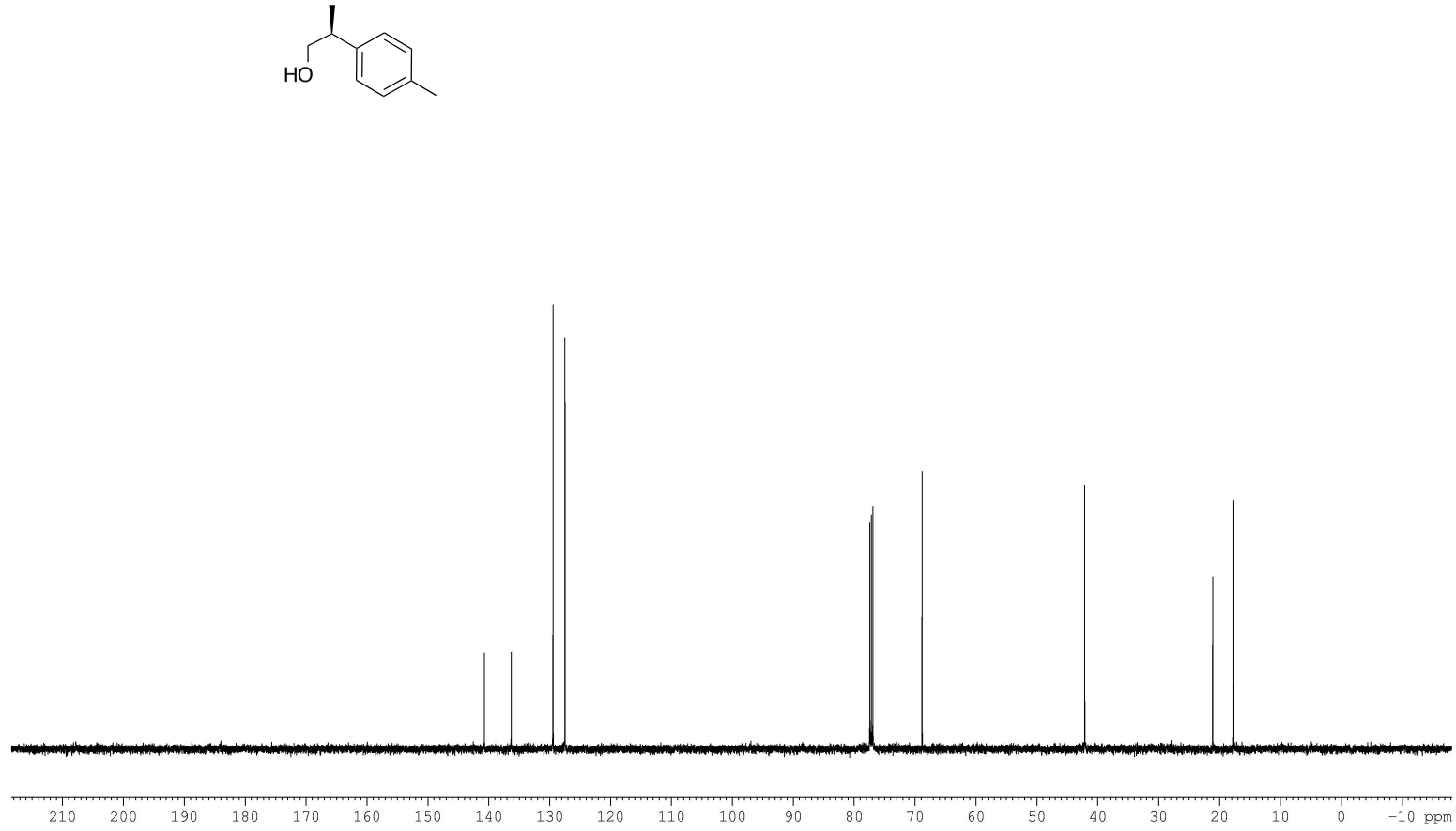



**Figure A1-8:** The 125 MHz $^{13}C$ NMR Spectrum of (–)-**2.12** in $CDCl_3$

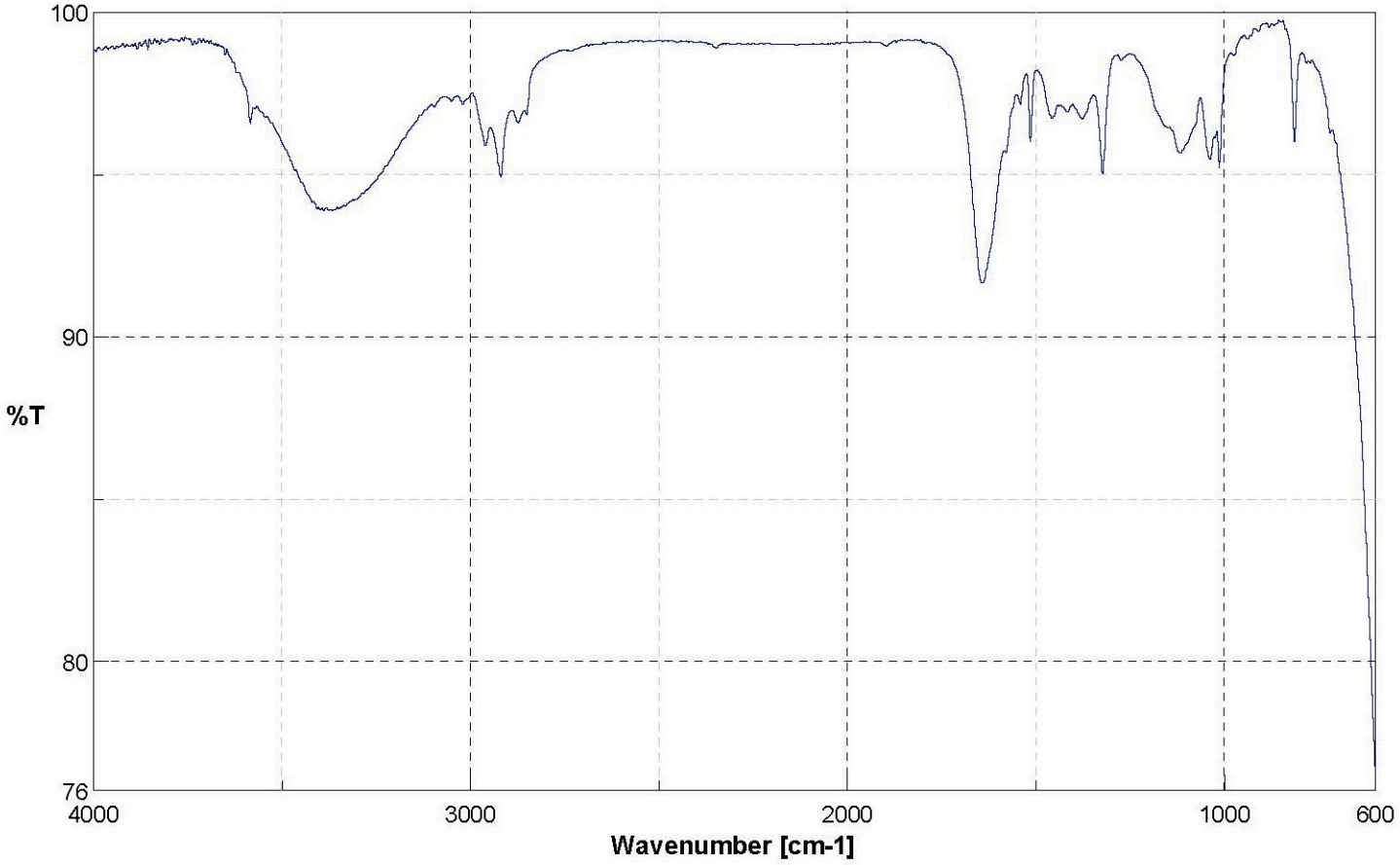



**Figure A1-9:** The Infrared Spectrum of Compound (–)-**2.12**

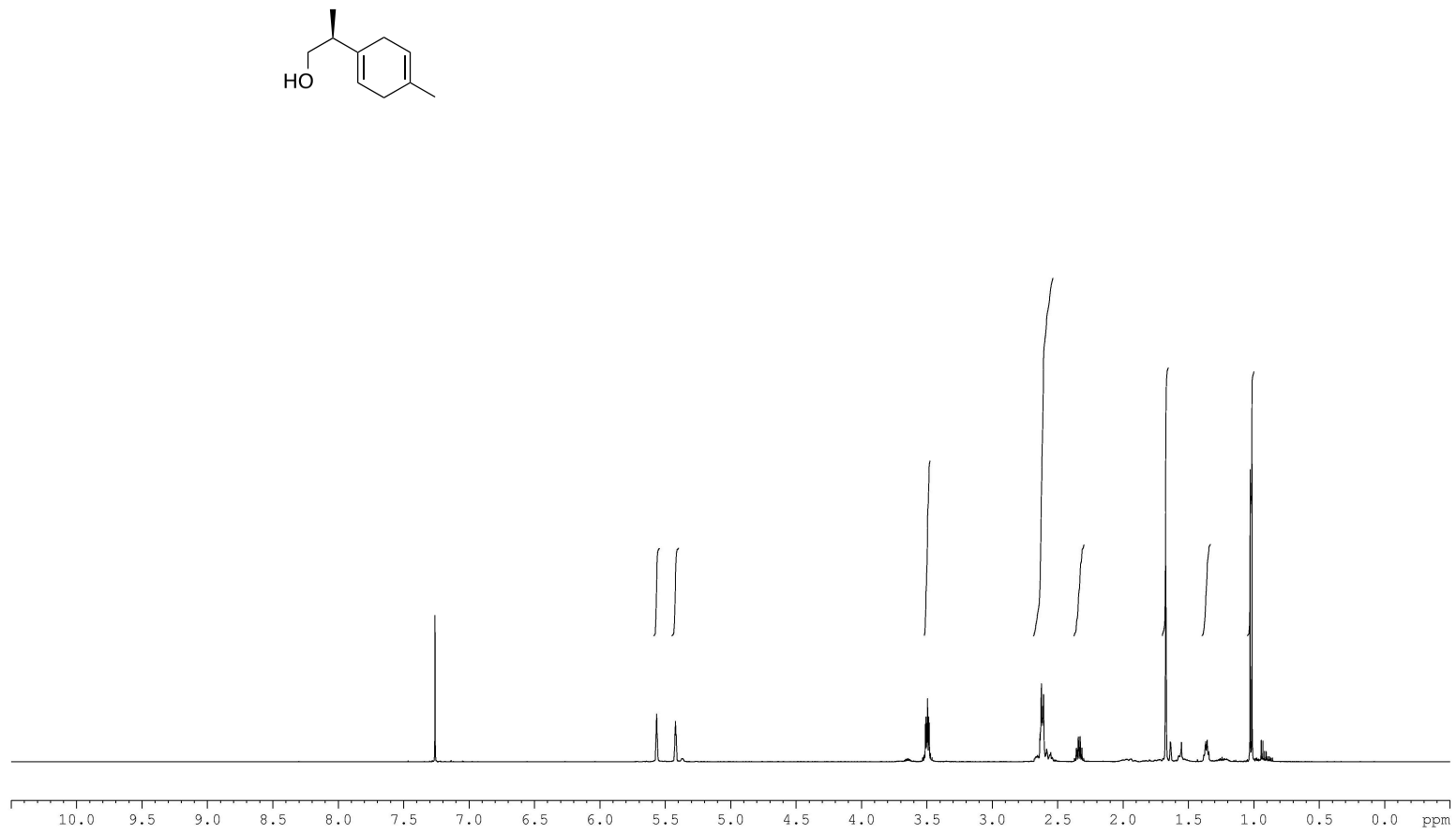



**Figure A1-10:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.13** in $CDCl_3$

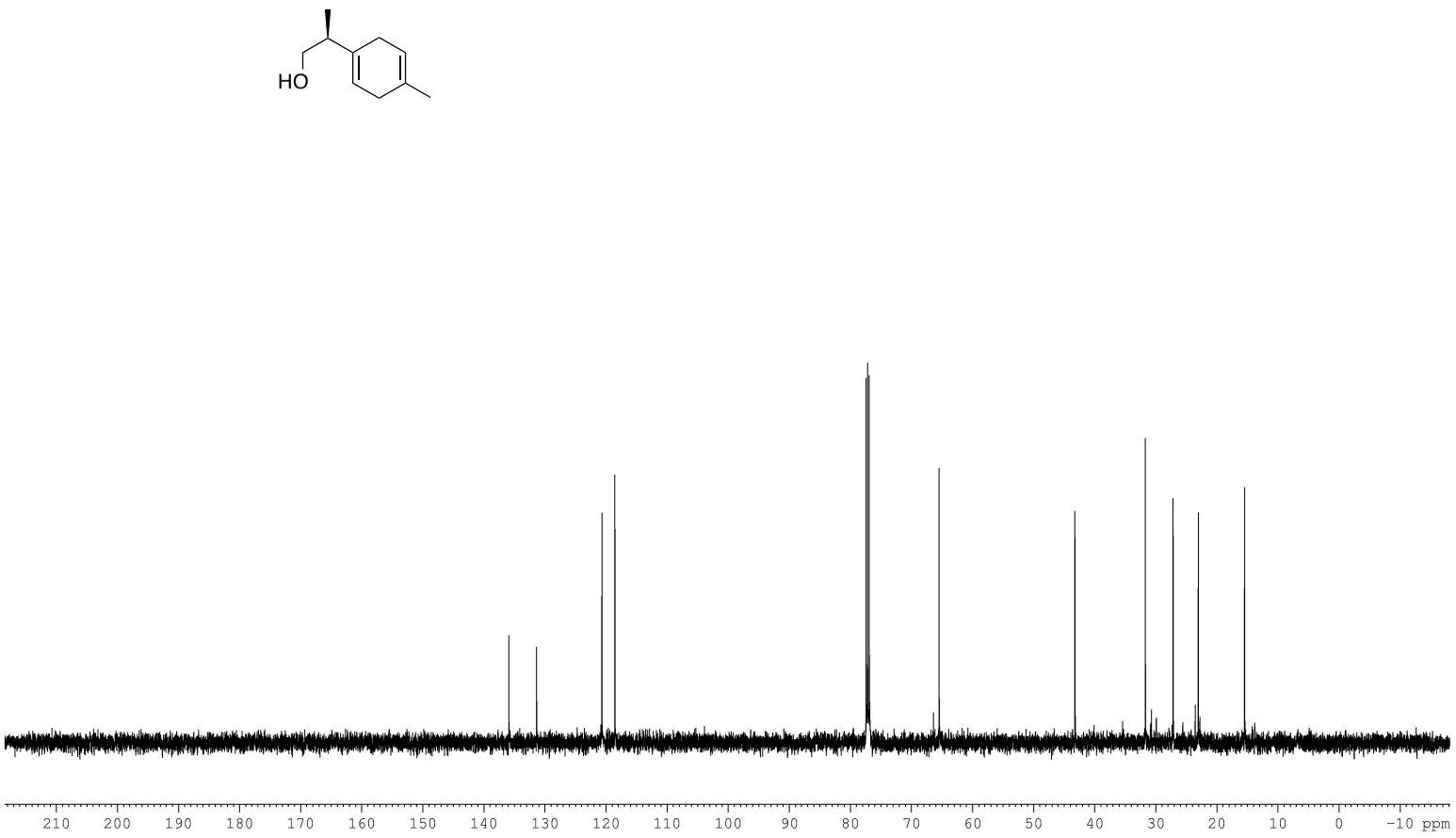



**Figure A1-11:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.13** in $CDCl_3$

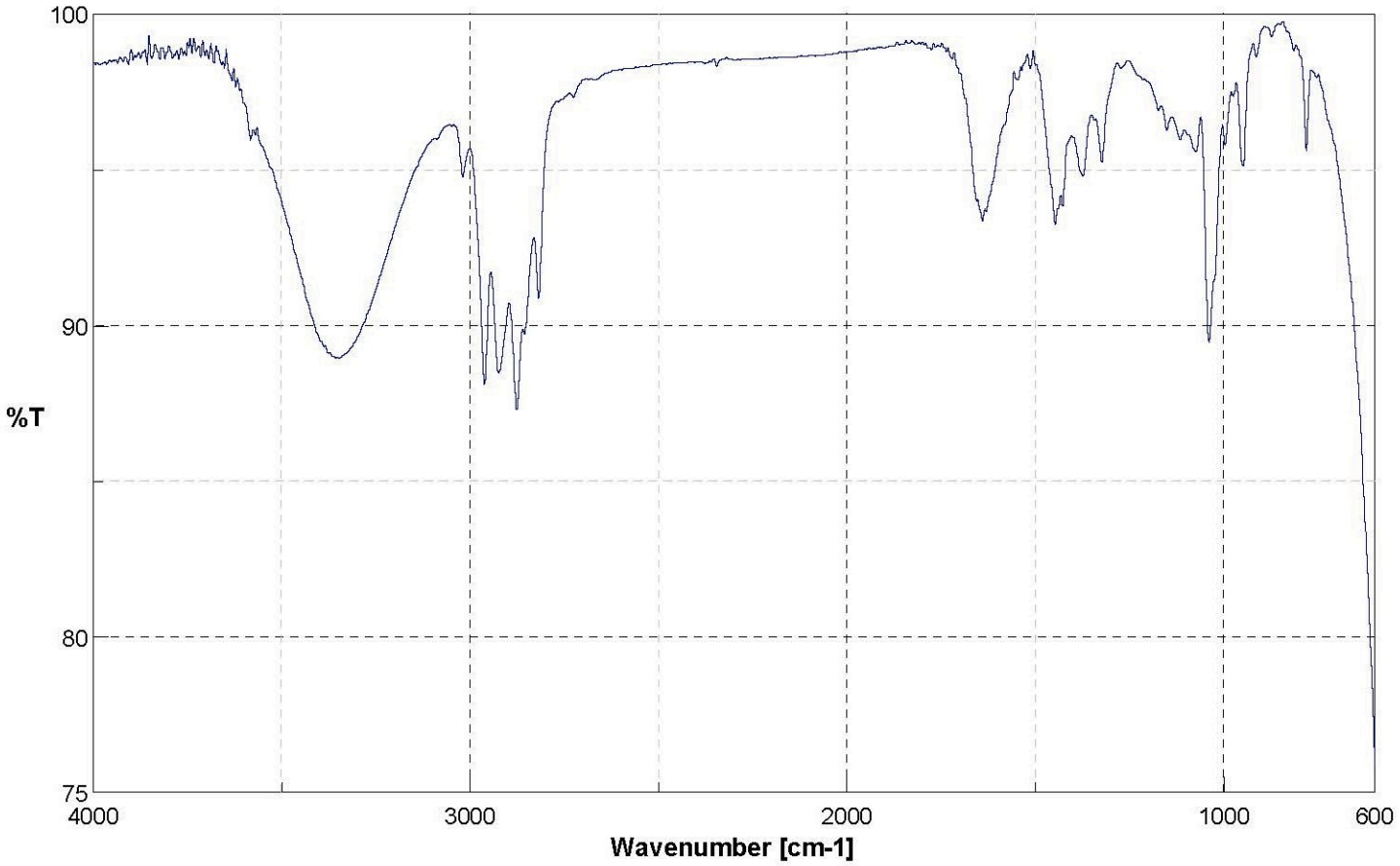



**Figure A1-12:** The Infrared Spectrum of Compound (–)-**2.13**

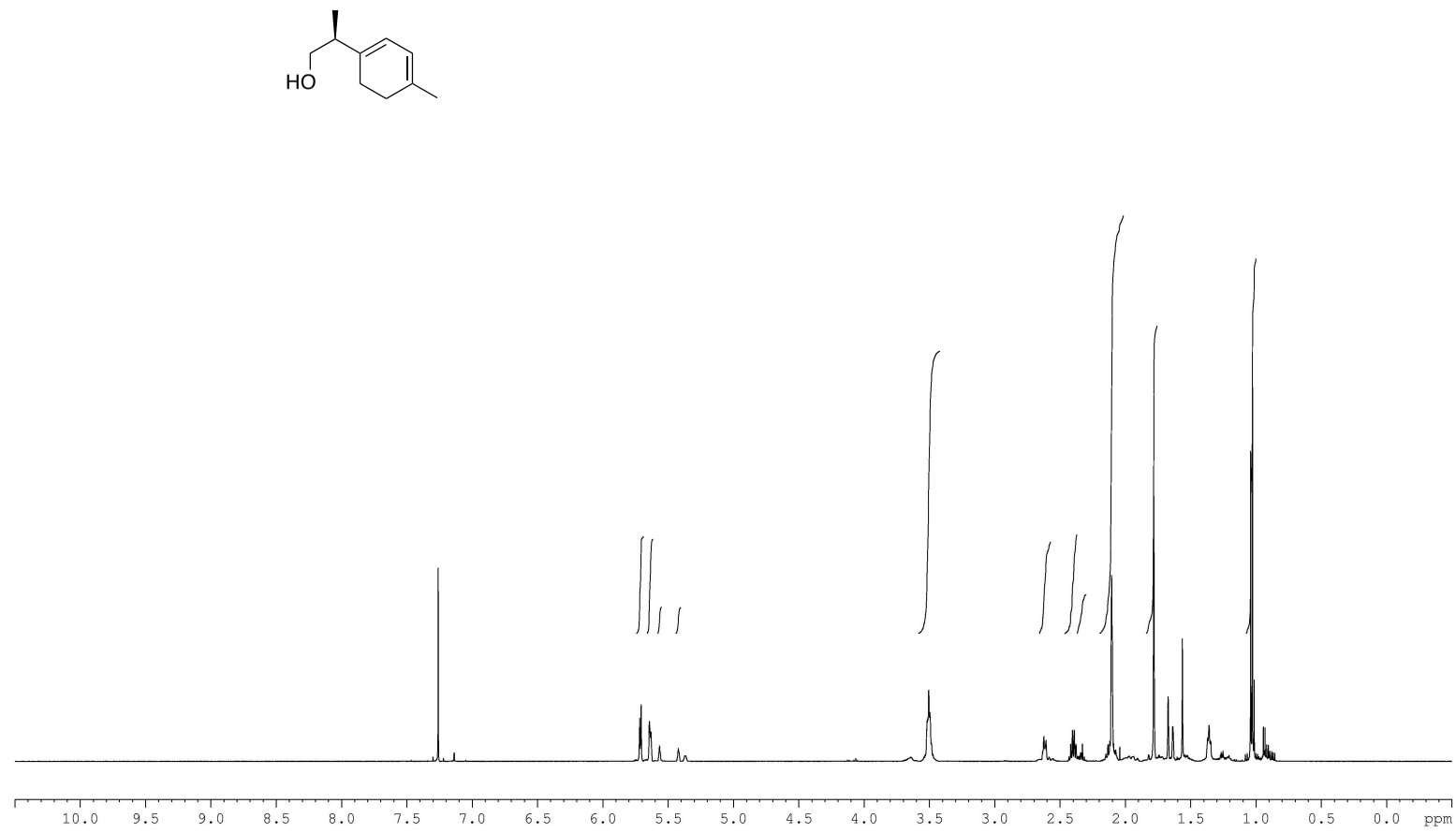



**Figure A1-13:** The 500 MHz $^{1}$H NMR Spectrum of Compounds [**2.6**:(–)-**2.13**] (3.5:1) in $CDCl_3$

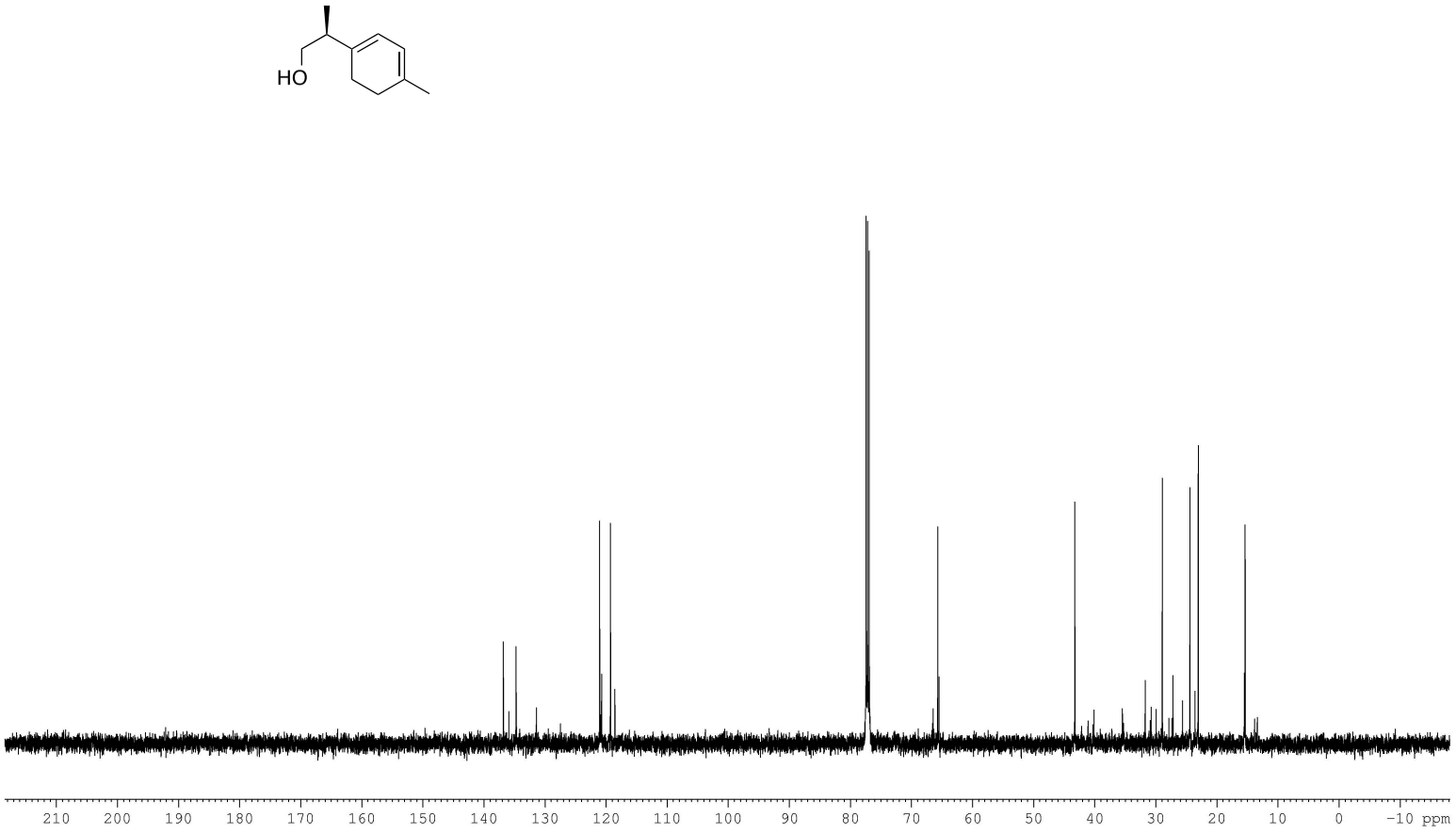



**Figure A1-14:** The 125 MHz $^{13}C$ NMR Spectrum of Compounds [**2.6**:(–)-**2.13**] (3.5:1) in $CDCl_3$

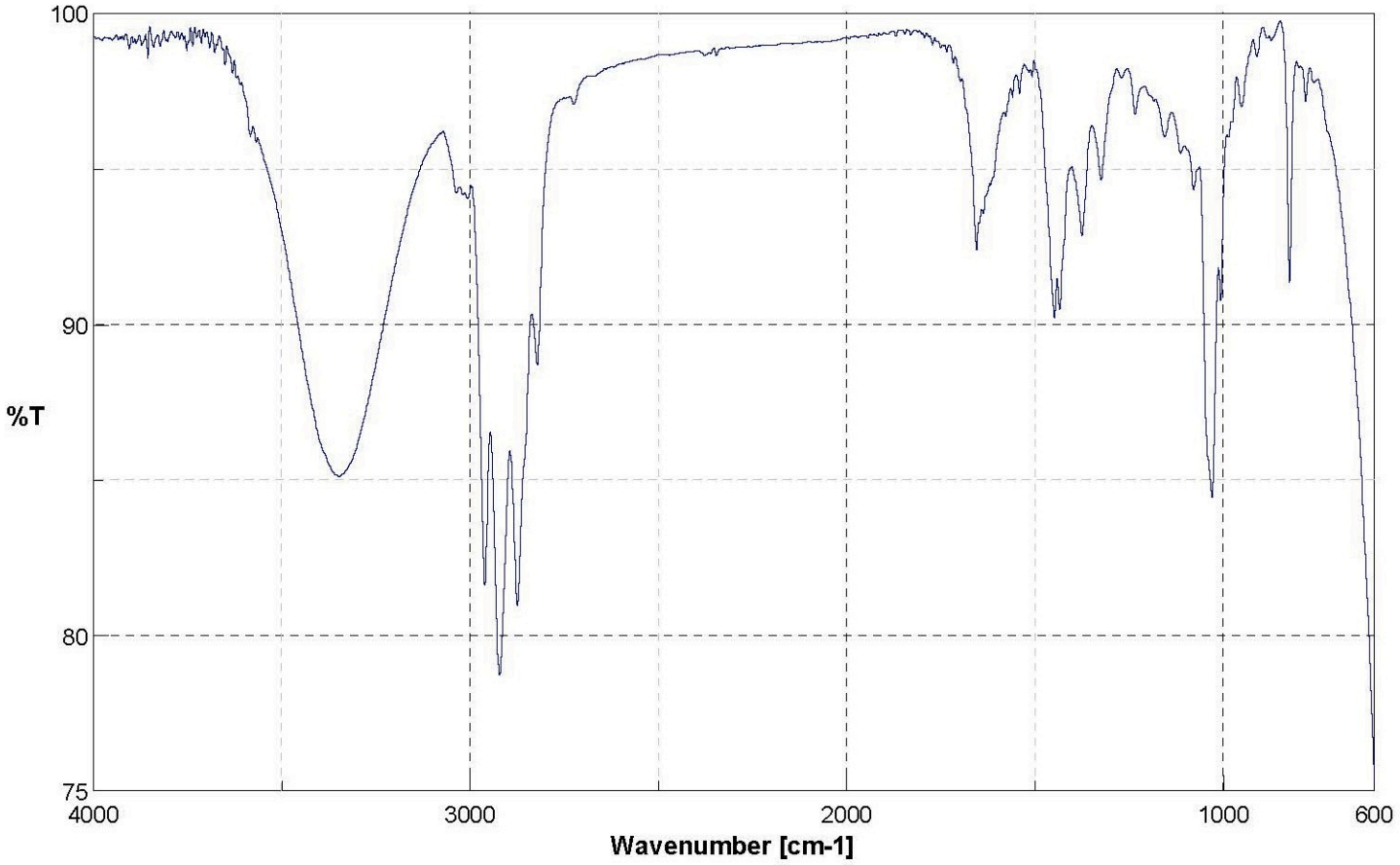



**Figure A1-15:** The Infrared Spectrum of Compounds [**2.6**:(–)-**2.13**] (3.5:1)

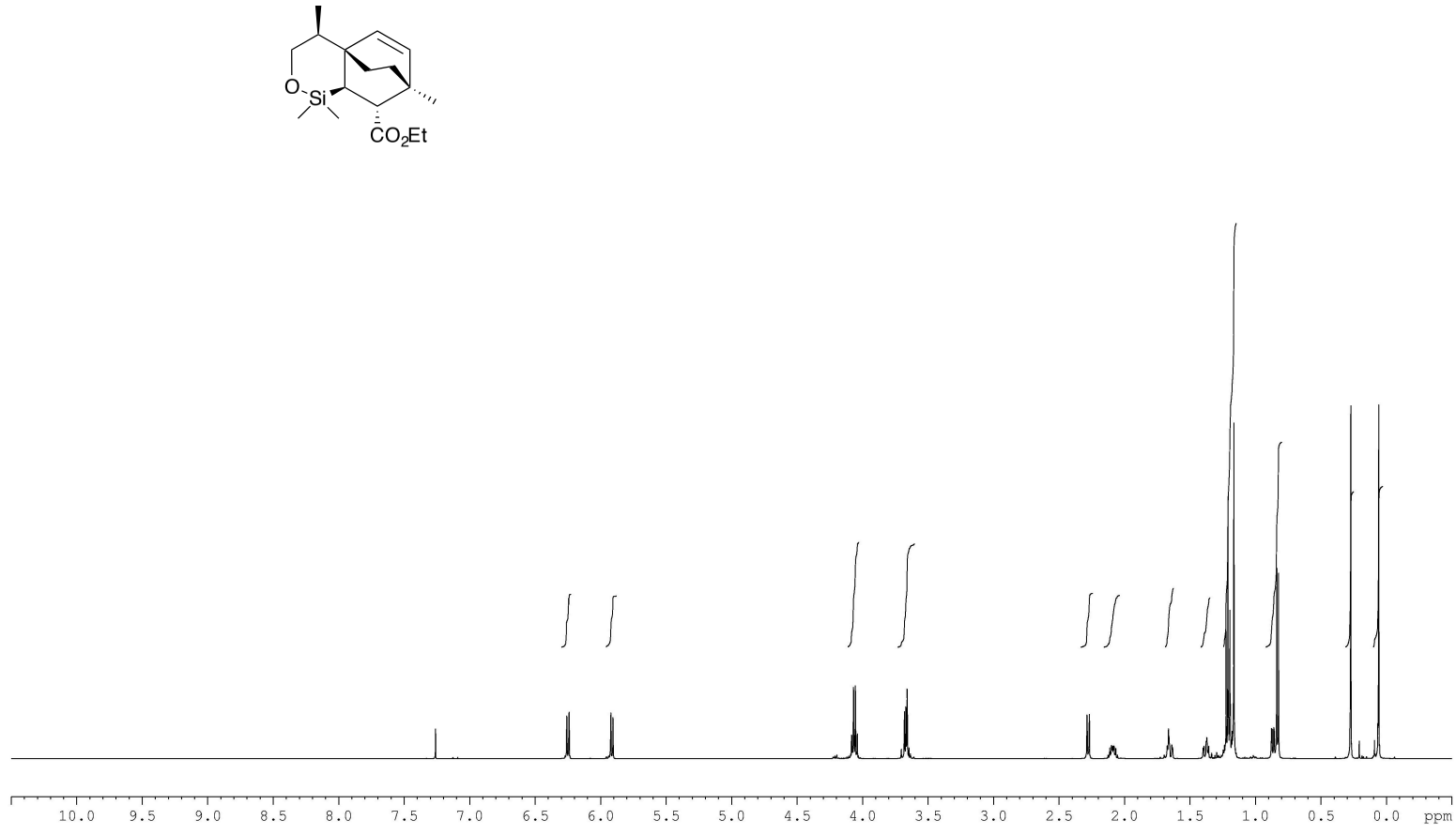



**Figure A1-16:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.4** in $CDCl_3$

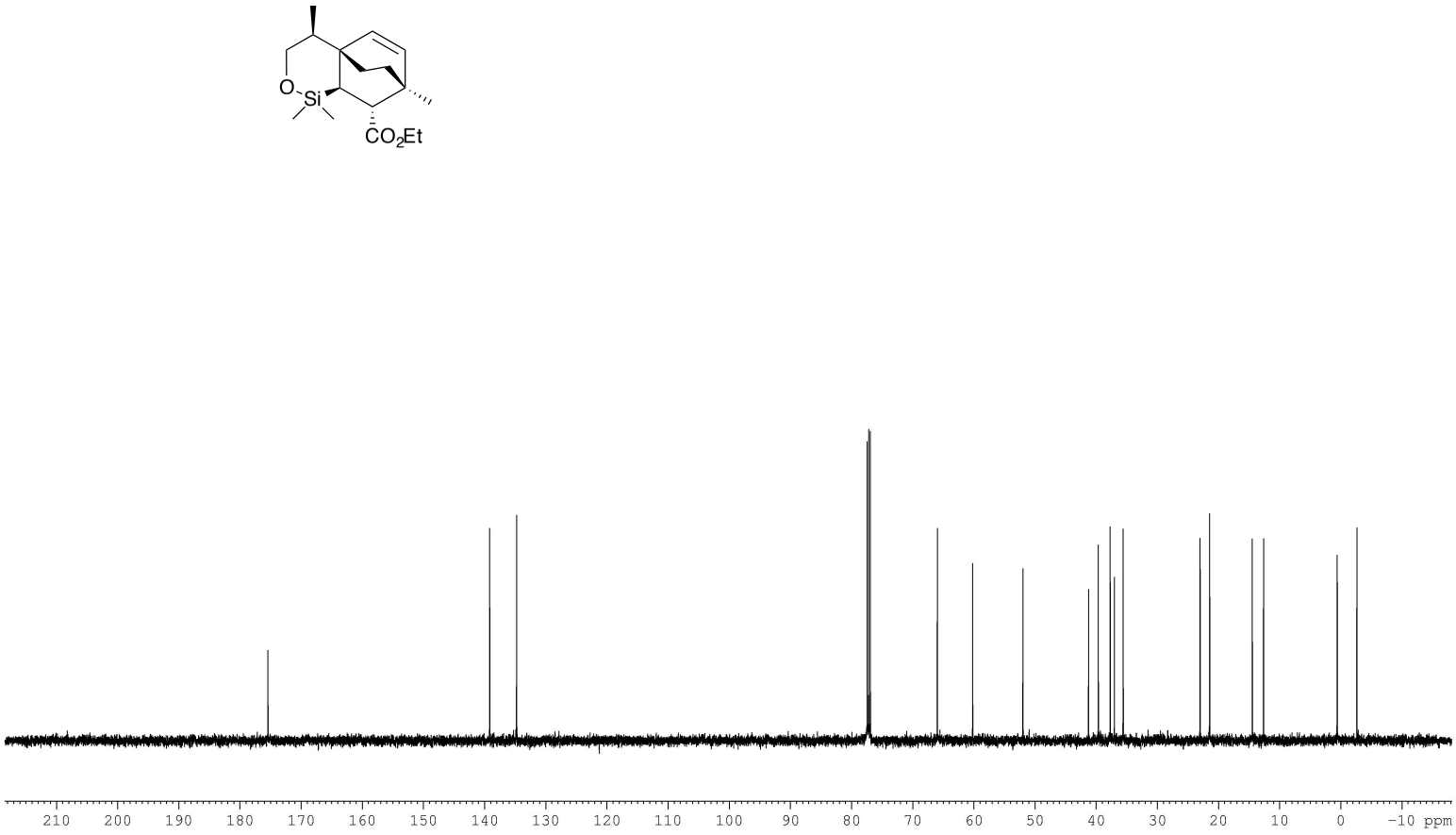



**Figure A1-17:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.4** in $CDCl_3$

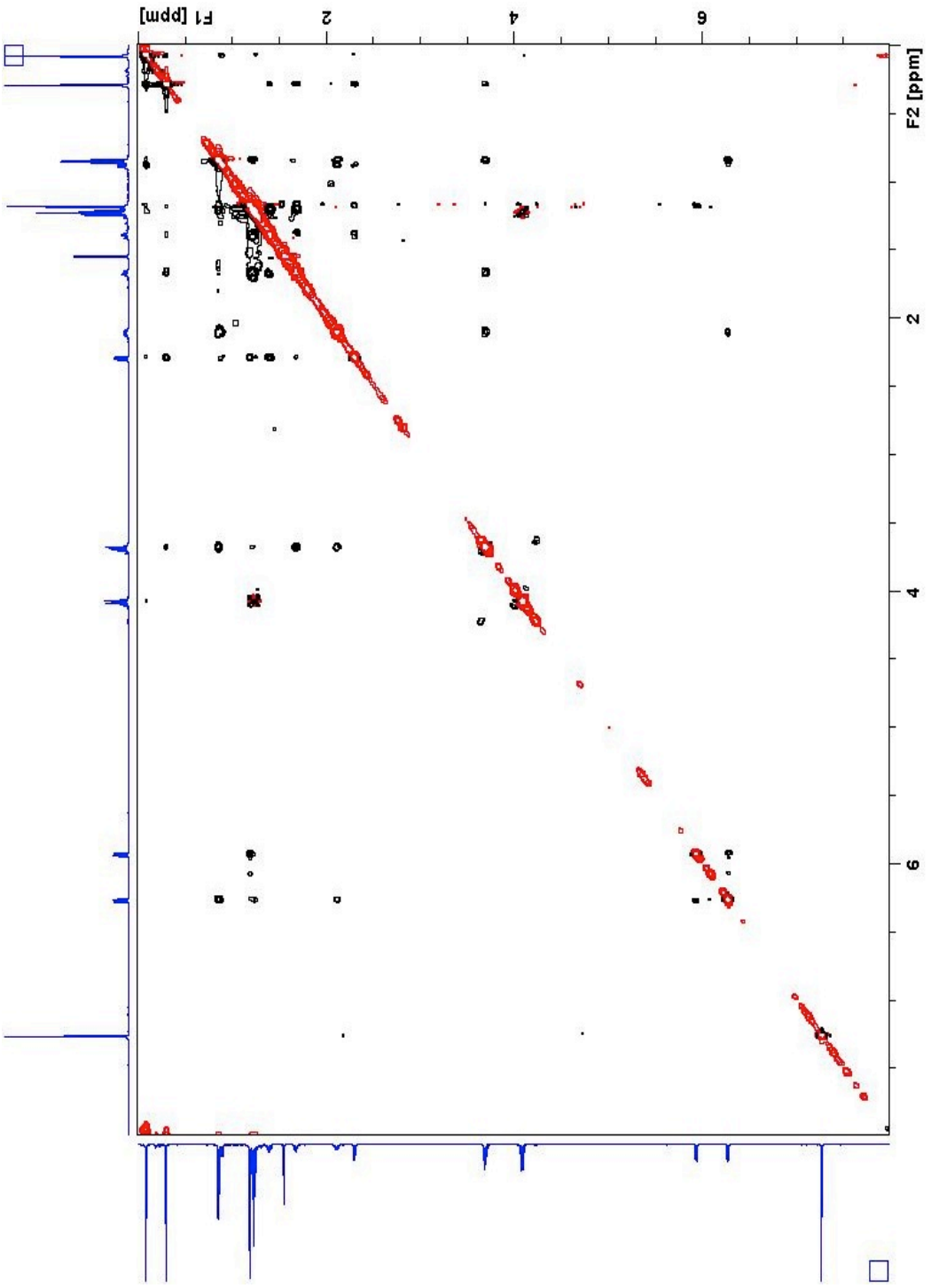



**Figure A1-18-:** The NOESY Spectrum of Compound (–)-**2.4** in $CDCl_3$

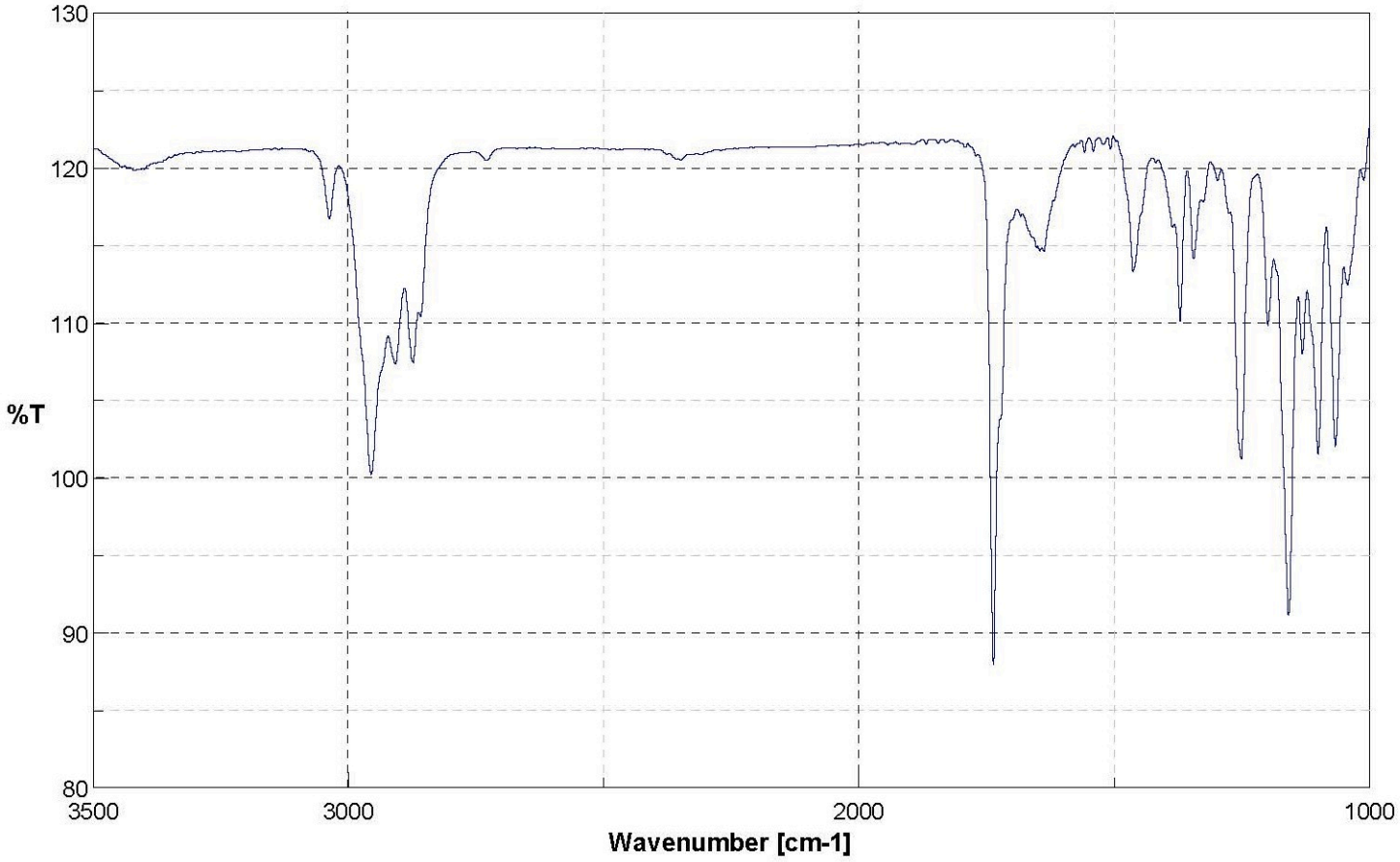



**Figure A1-19:** The Infrared Spectrum of Compound (–)-**2.4**

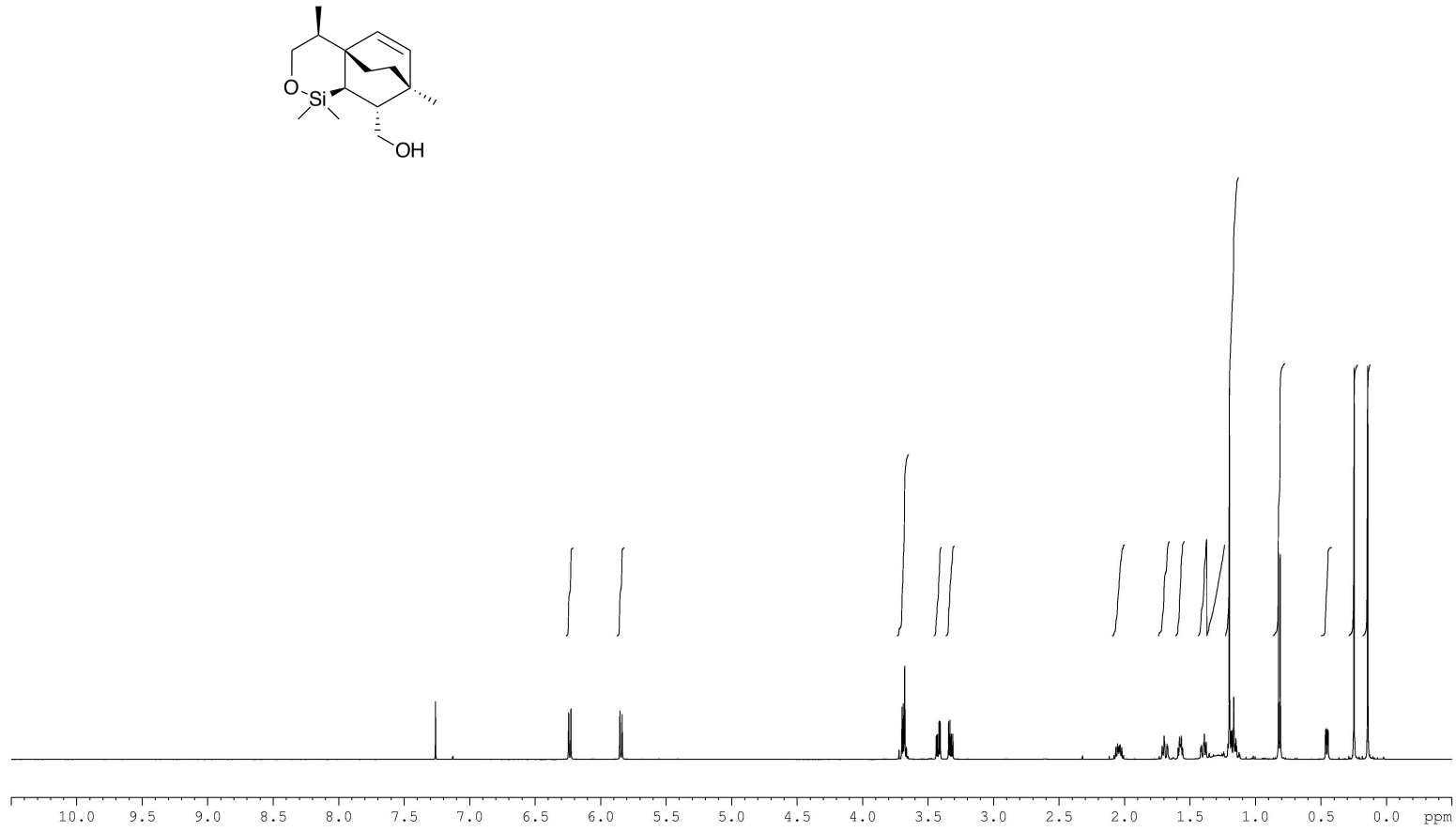



**Figure A1-20:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.16** in $CDCl_3$

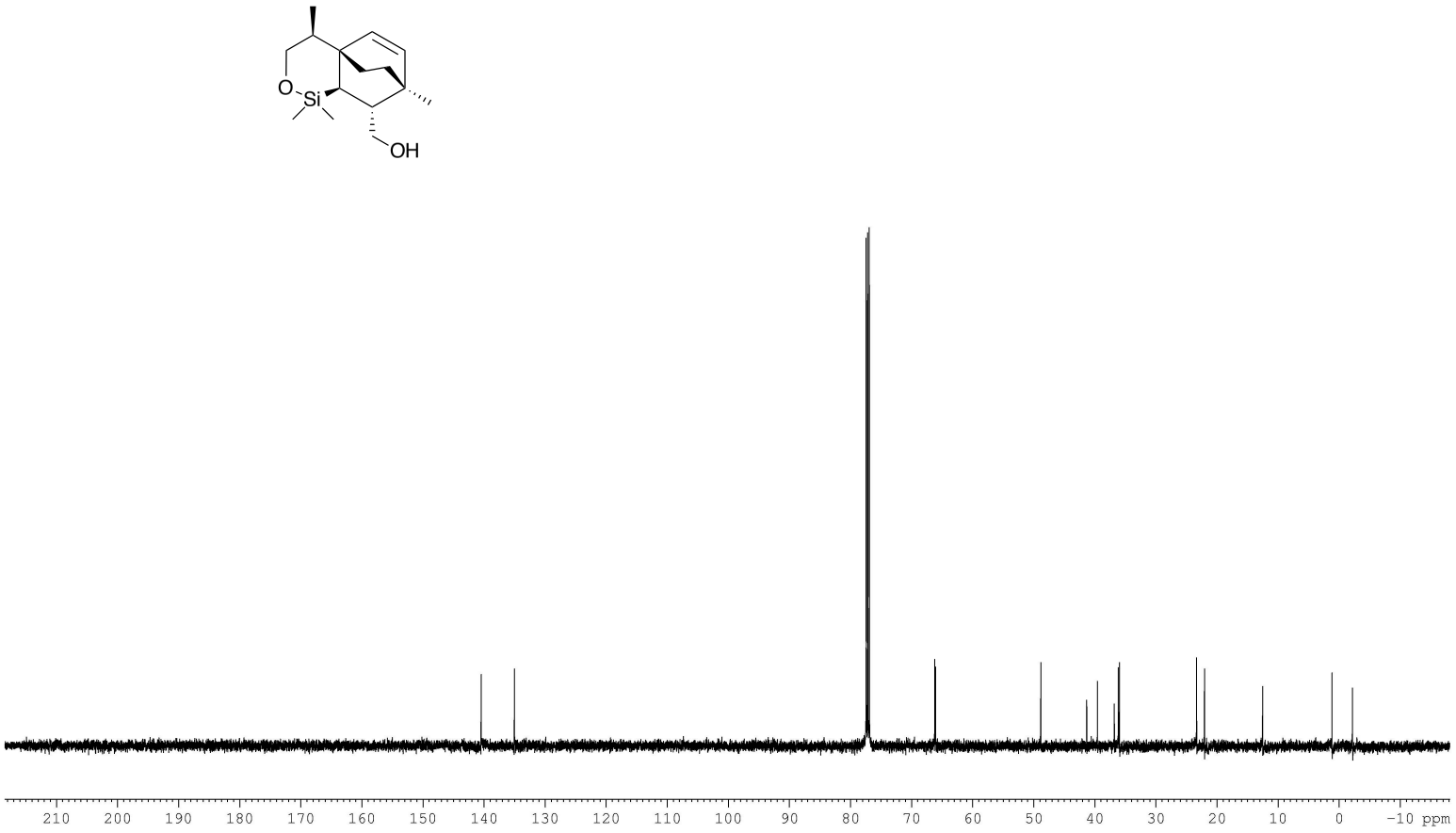



**Figure A1-21:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.16** in $CDCl_3$

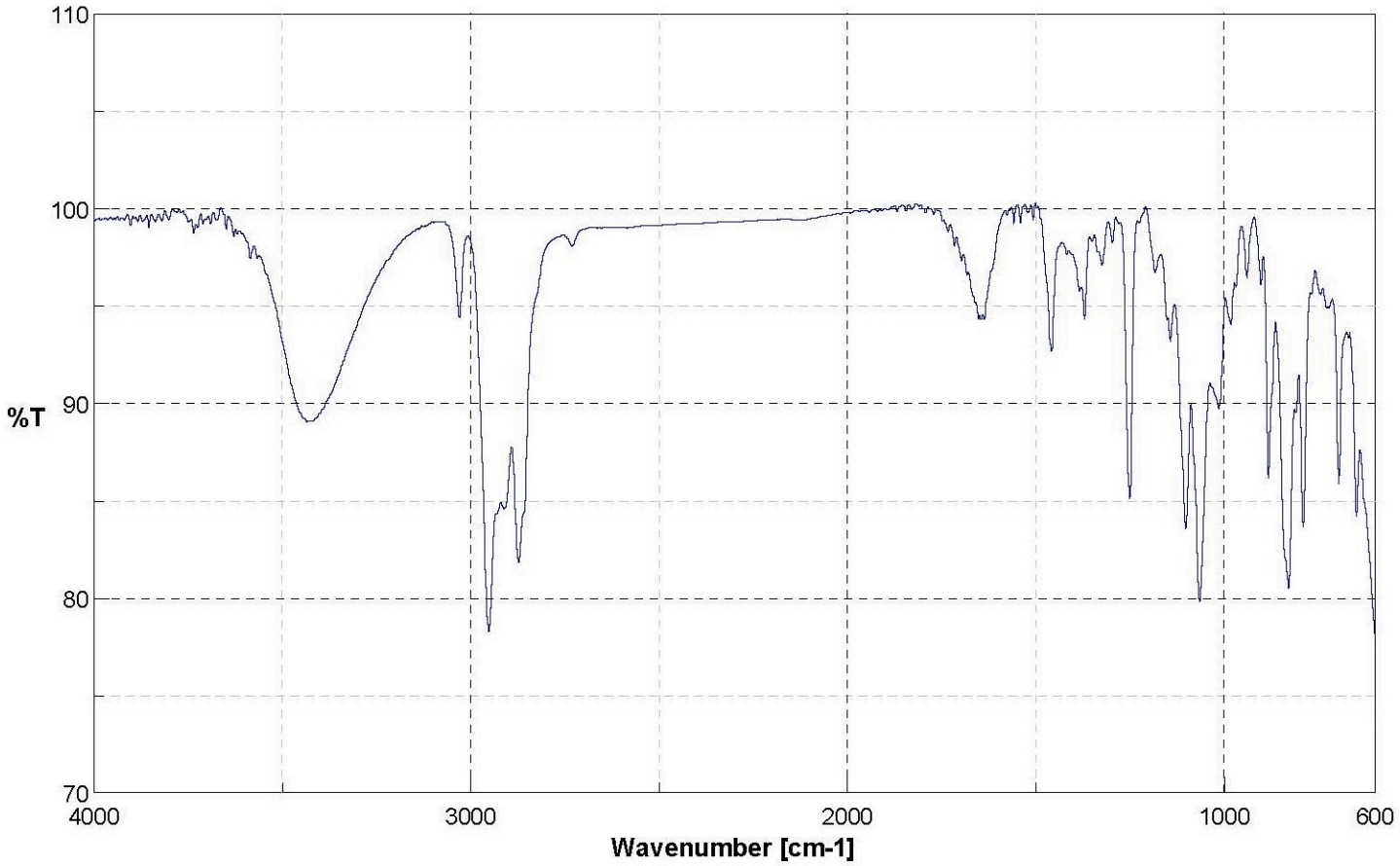



**Figure A1-22:** The Infrared Spectrum of Compound (–)-**2.16**

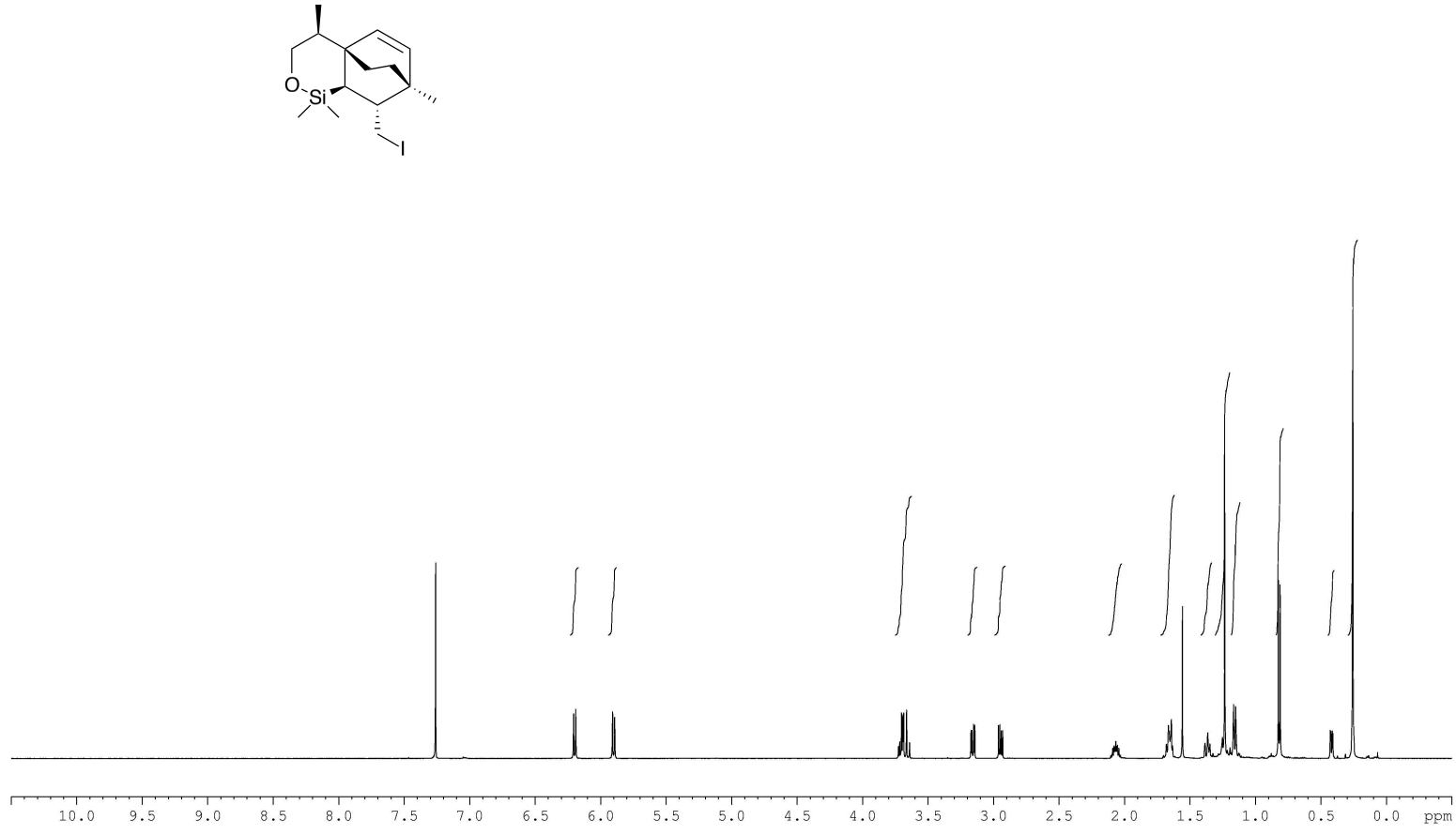



**Figure A1-23:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.17** in $CDCl_3$

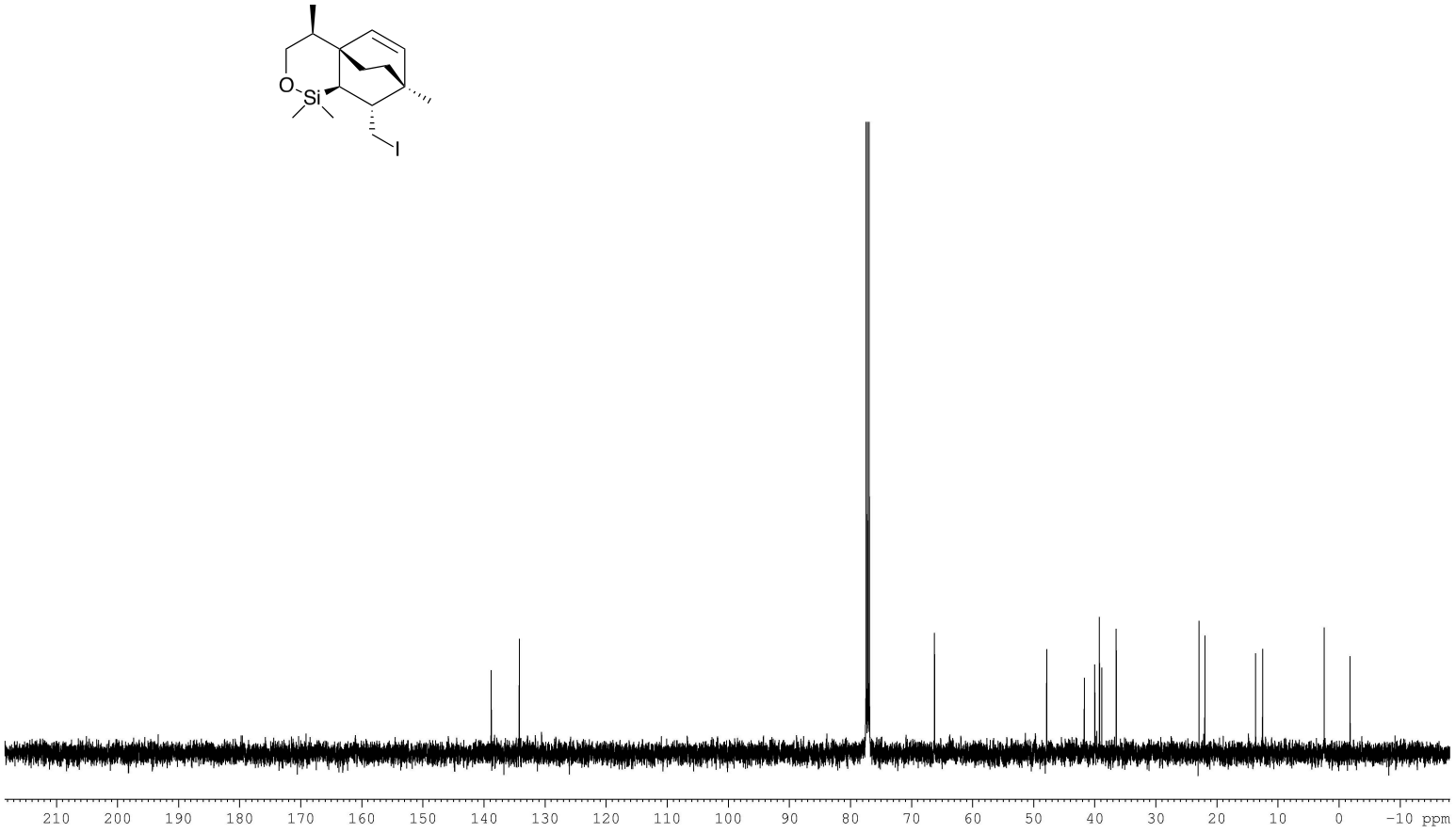



**Figure A1-24:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.17** in $CDCl_3$

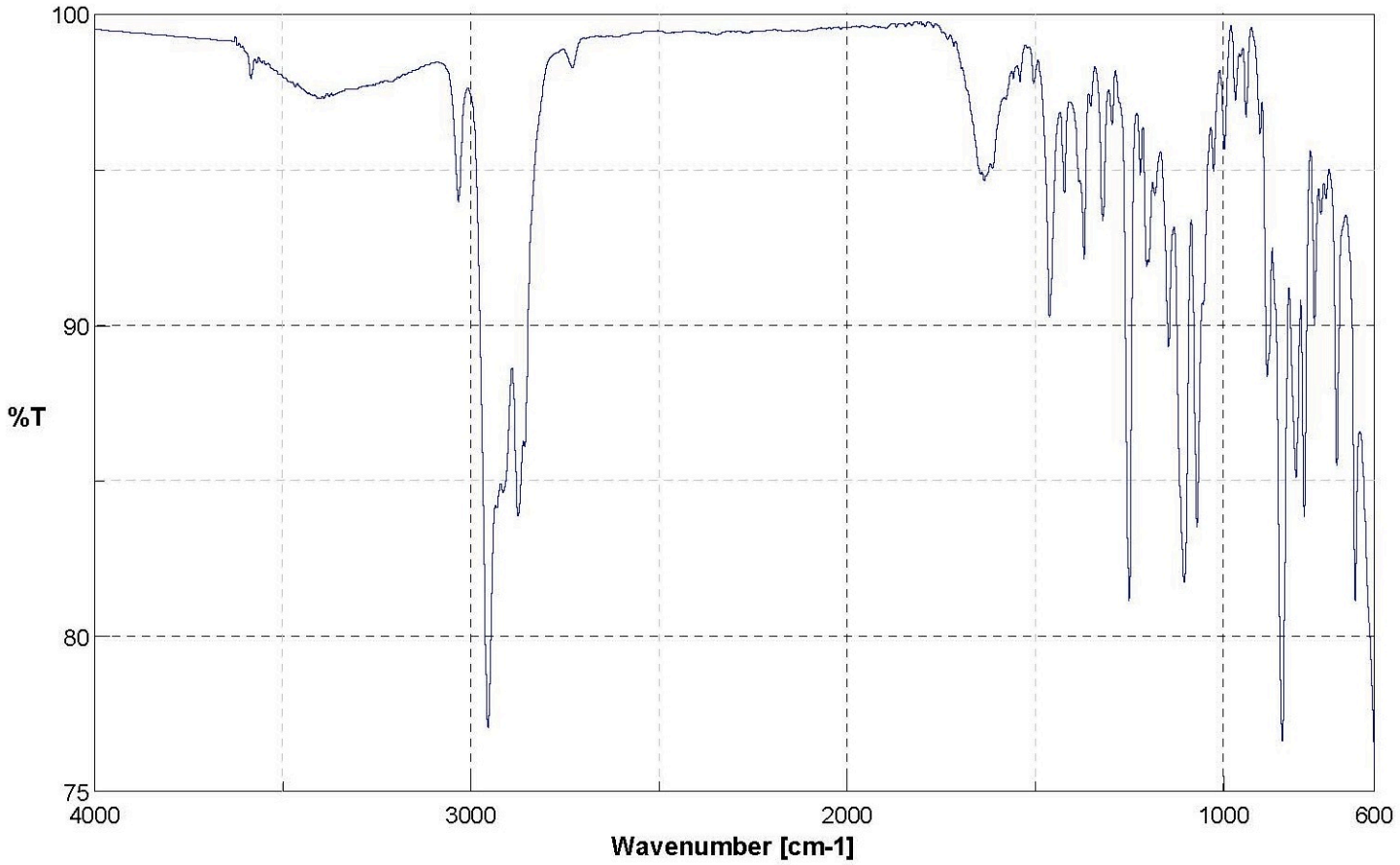



**Figure A1-25:** The Infrared Spectrum of Compound (–)-**2.17**

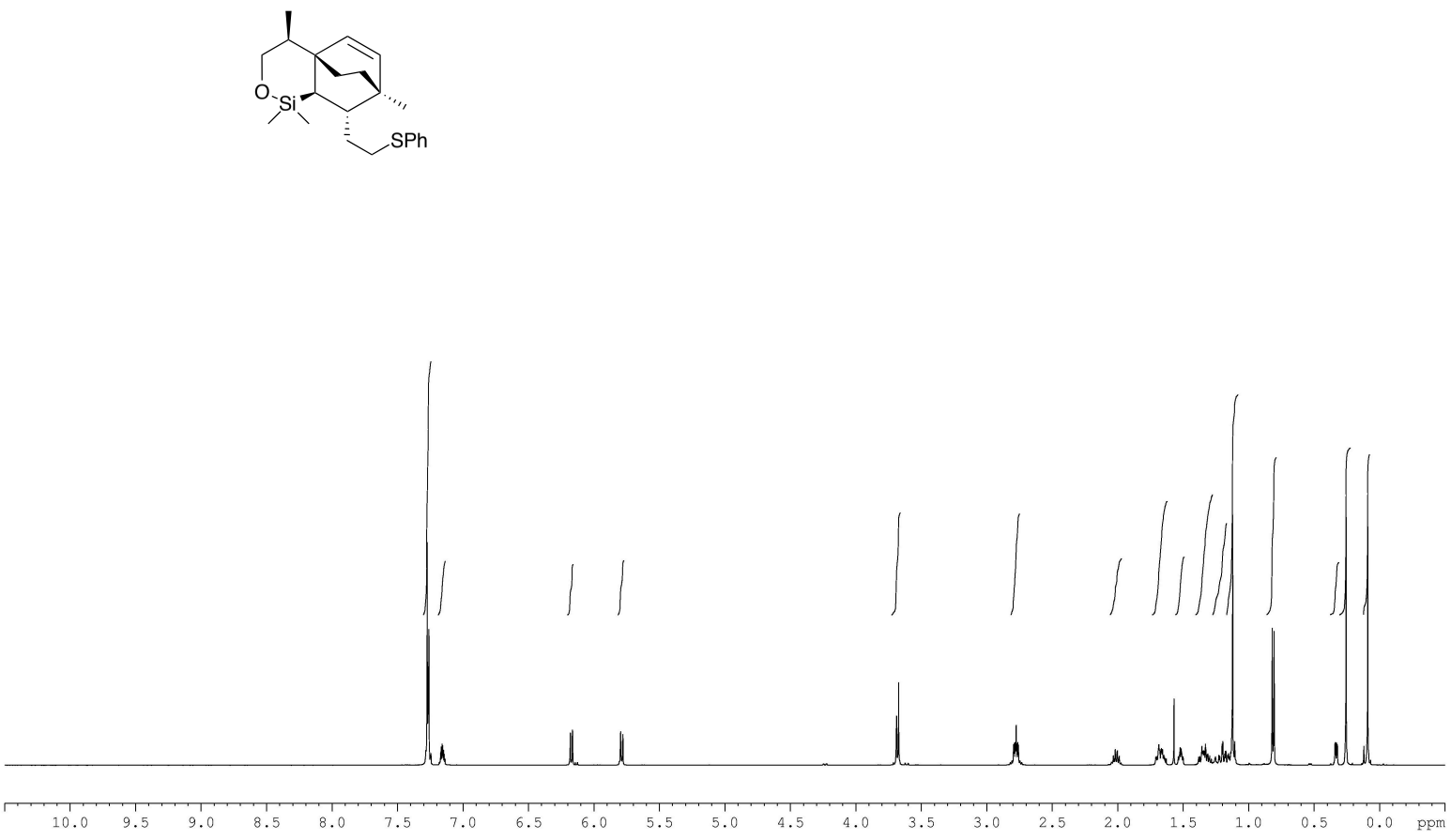



**Figure A1-26:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.18** in $CDCl_3$

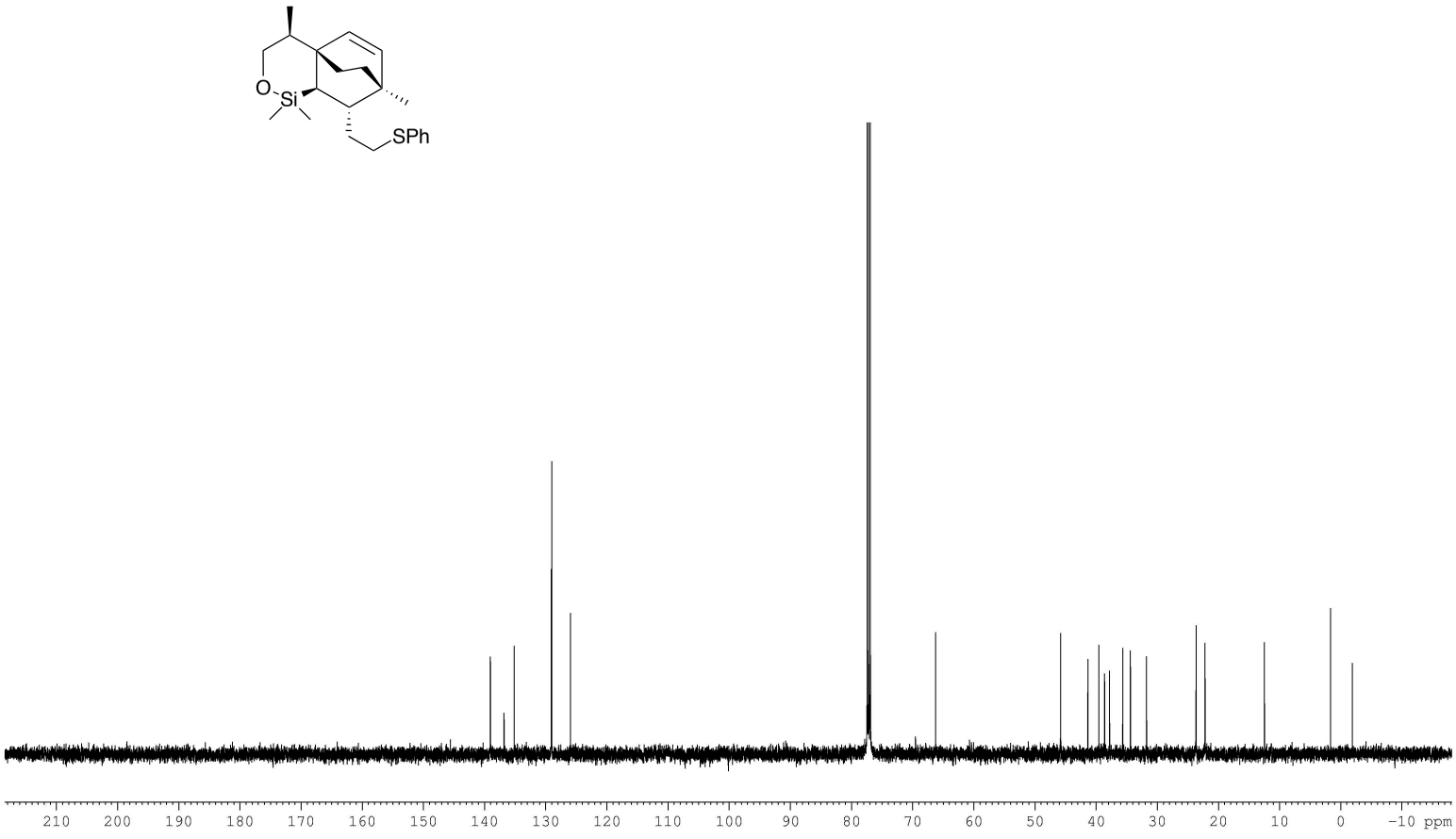



**Figure A1-27:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.18** in $CDCl_3$

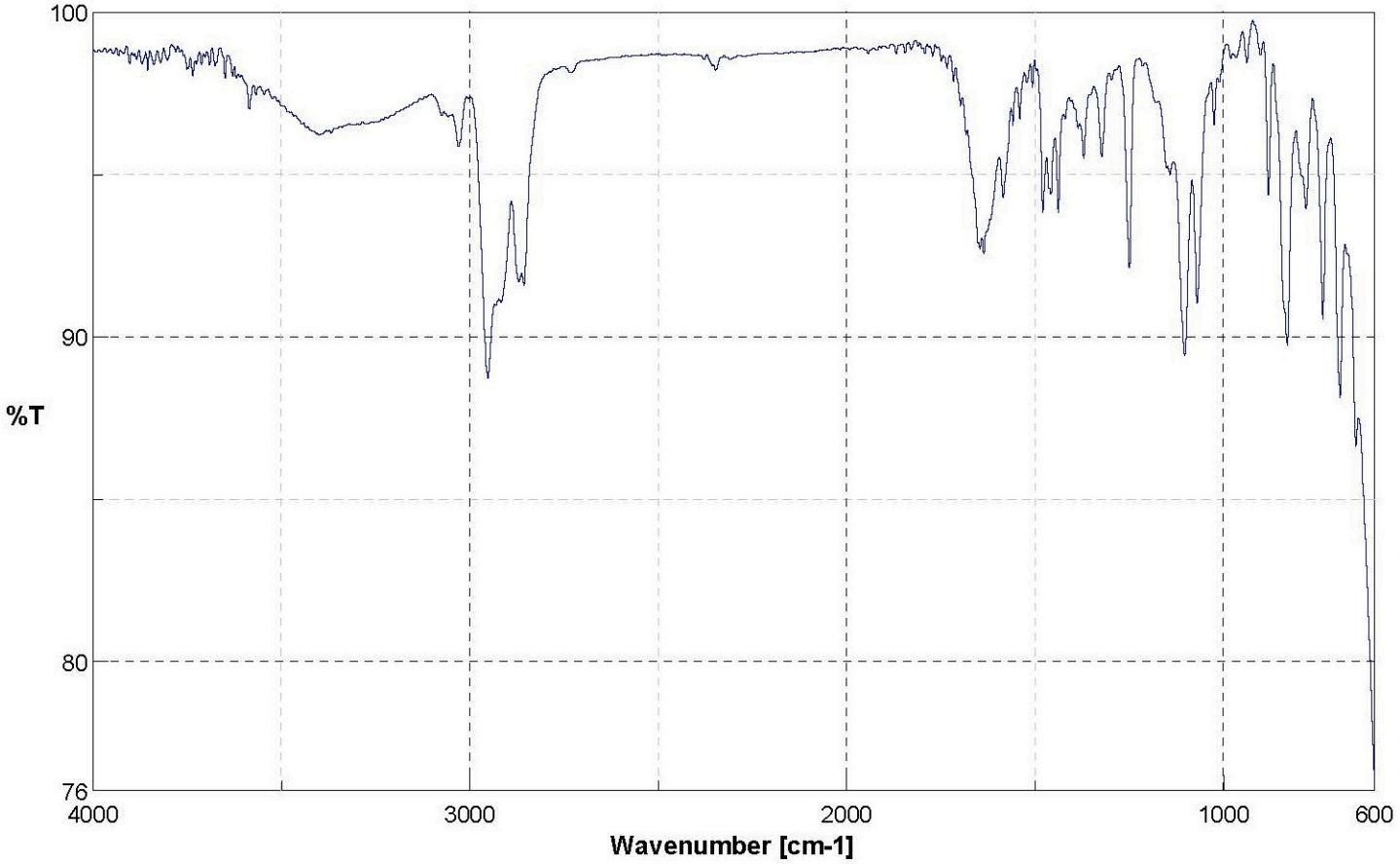



**Figure A1-28:** The Infrared Spectrum of Compound (–)-**2.18**

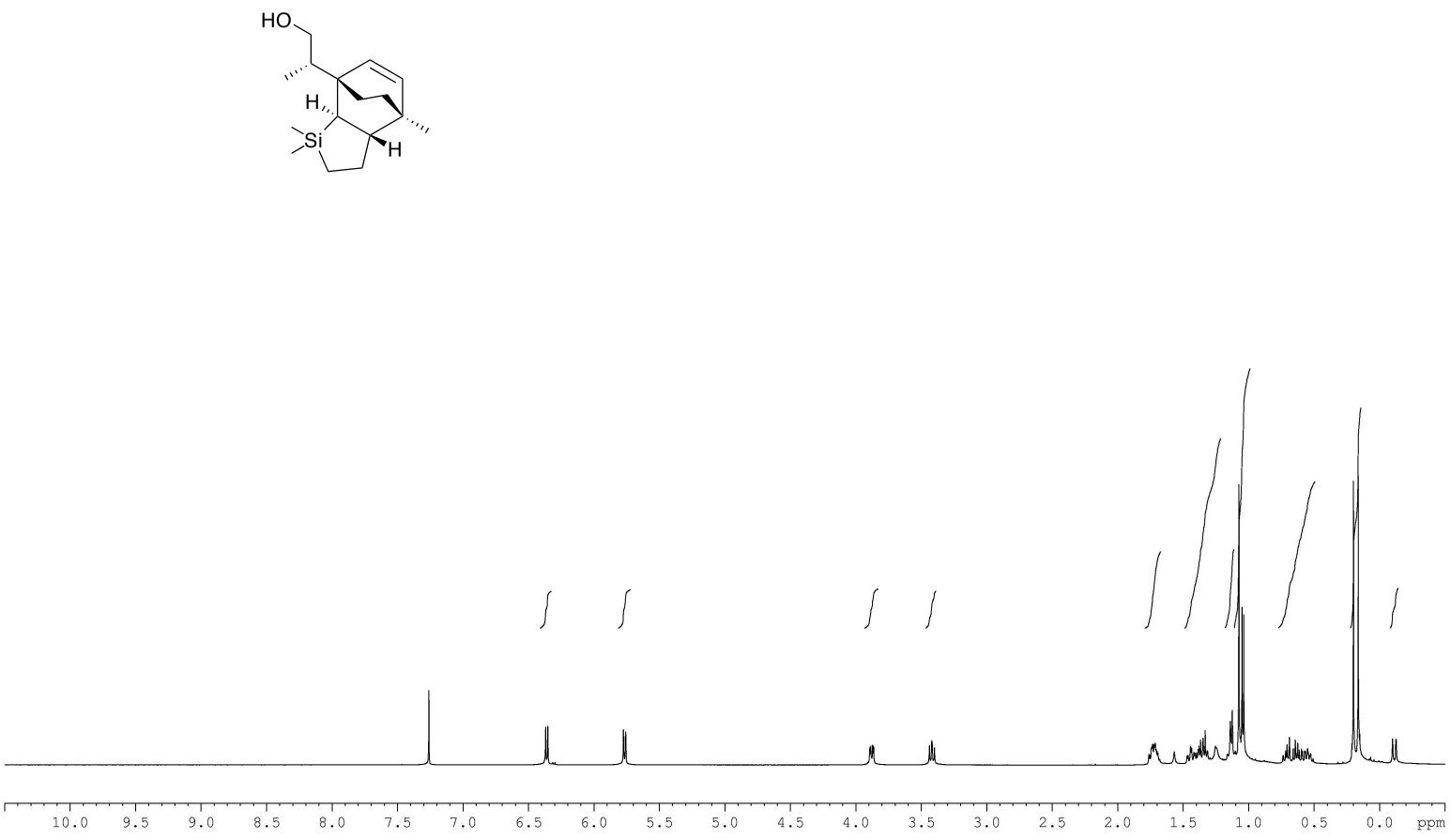



**Figure A1-29:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.21** in $CDCl_3$

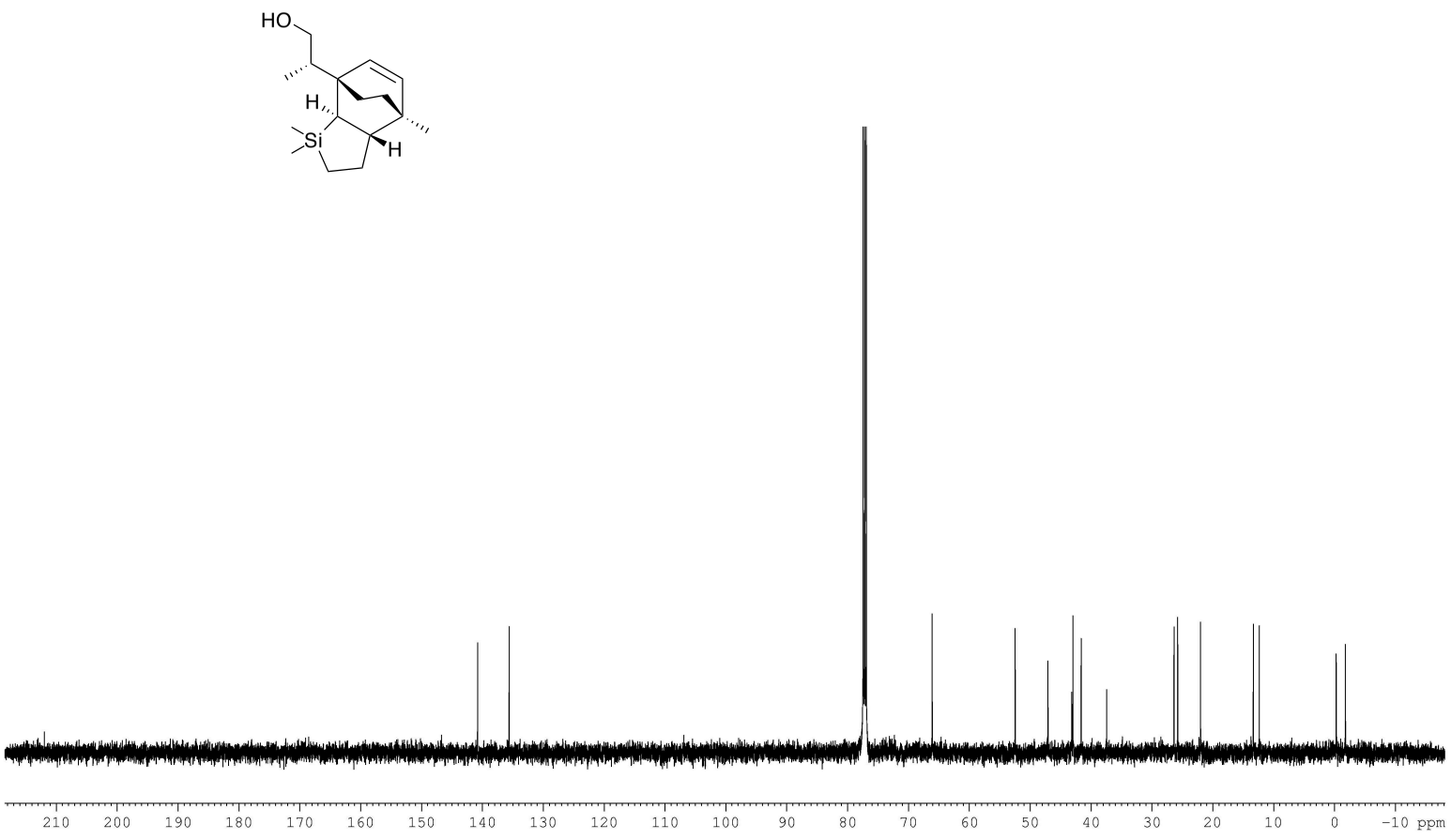



**Figure A1-30:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.21** in $CDCl_3$

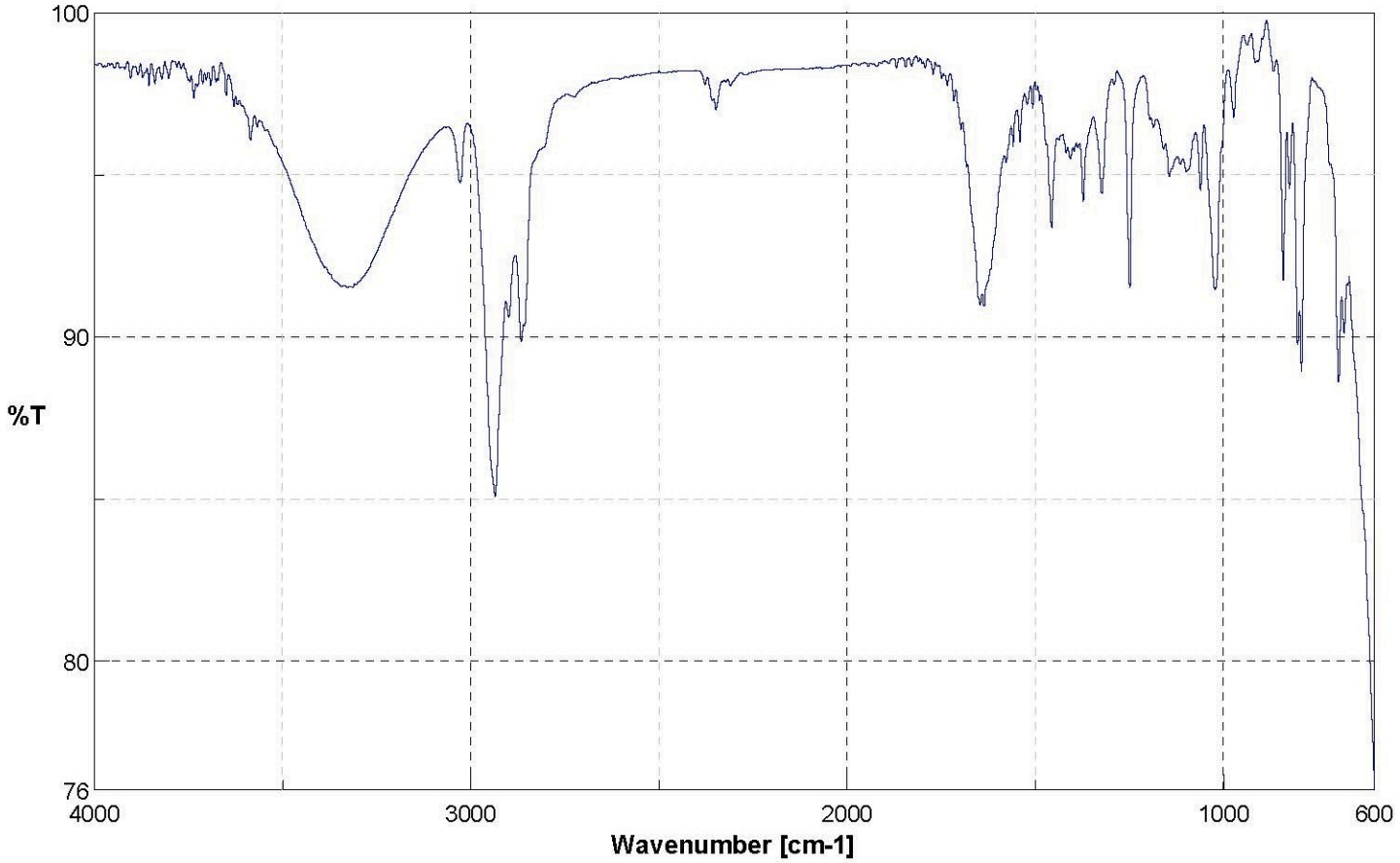



**Figure A1-31:** The Infrared Spectrum of Compound (–)-**2.21**

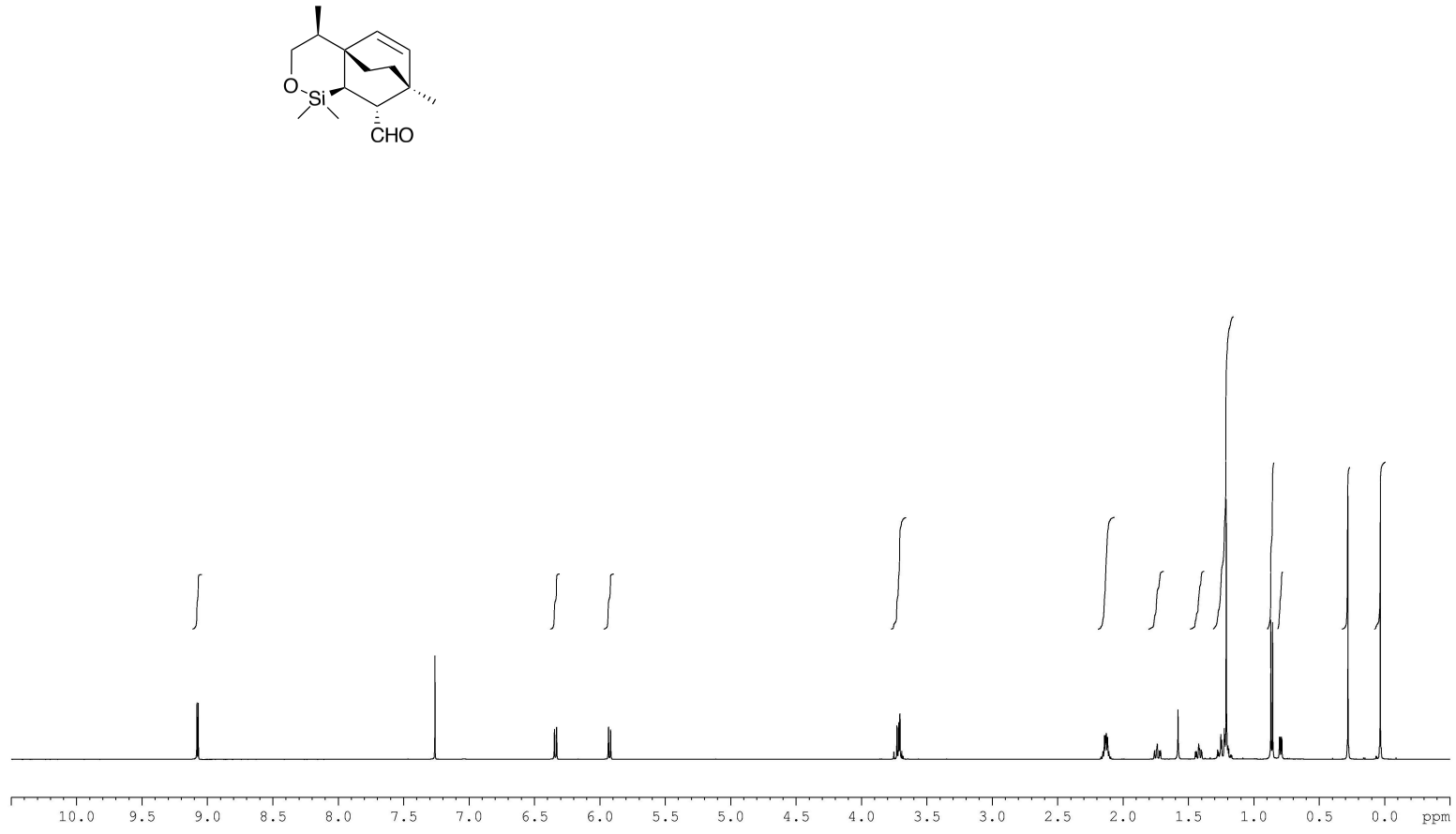



**Figure A1-32:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.22** in $CDCl_3$

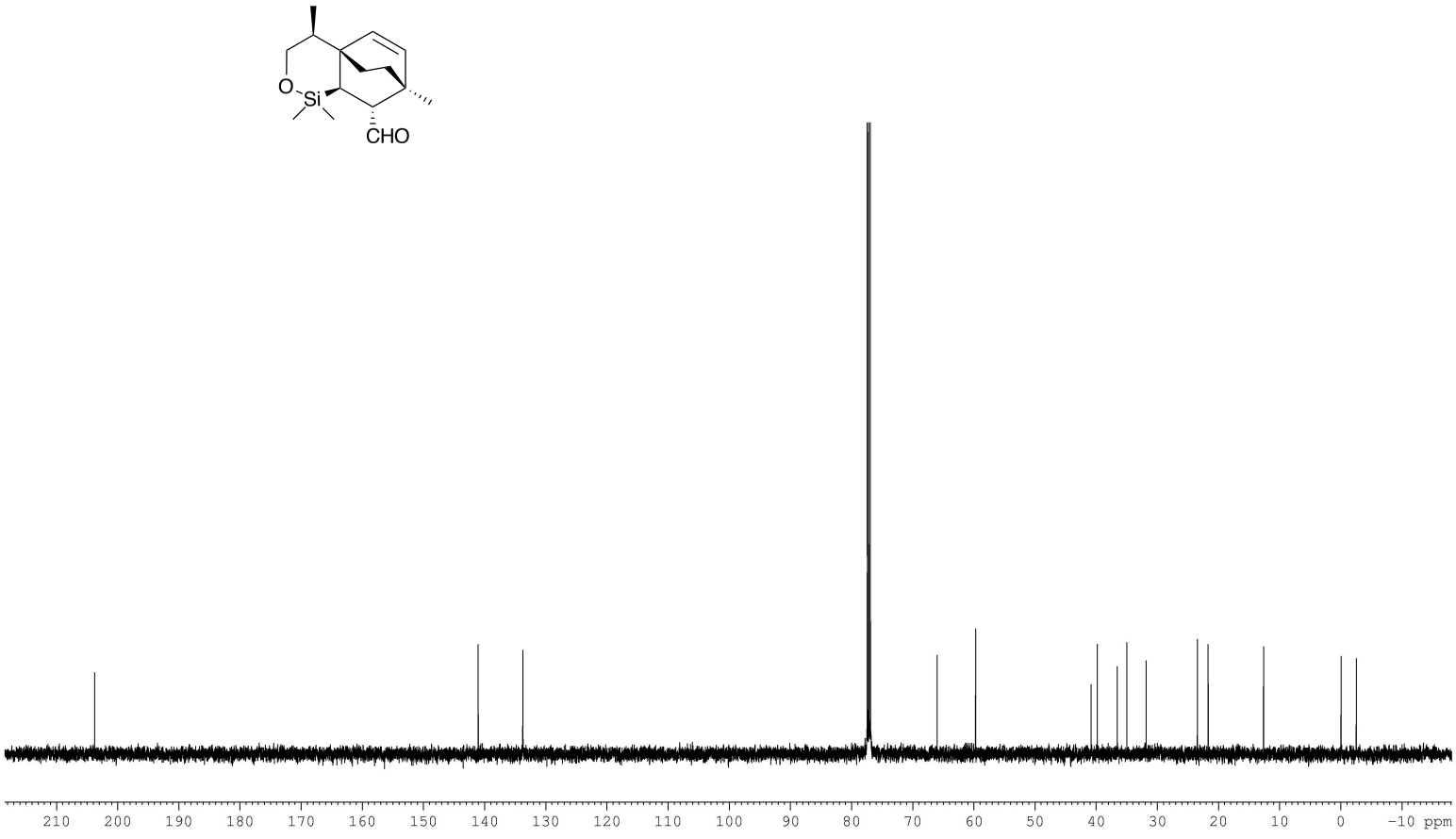



**Figure A1-33:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.22** in $CDCl_3$

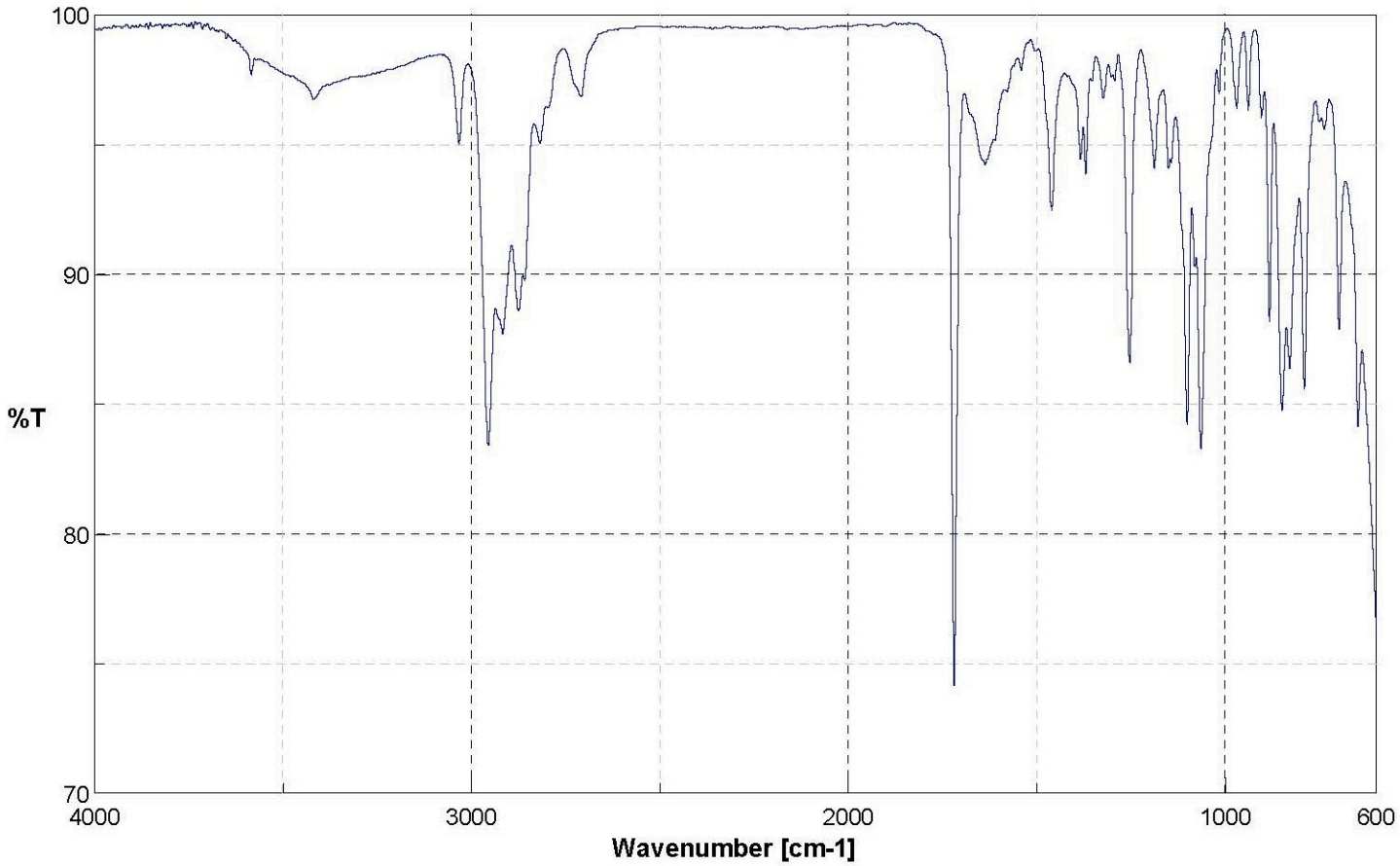



**Figure A1-34:** The Infrared Spectrum of Compound (–)-**2.22**

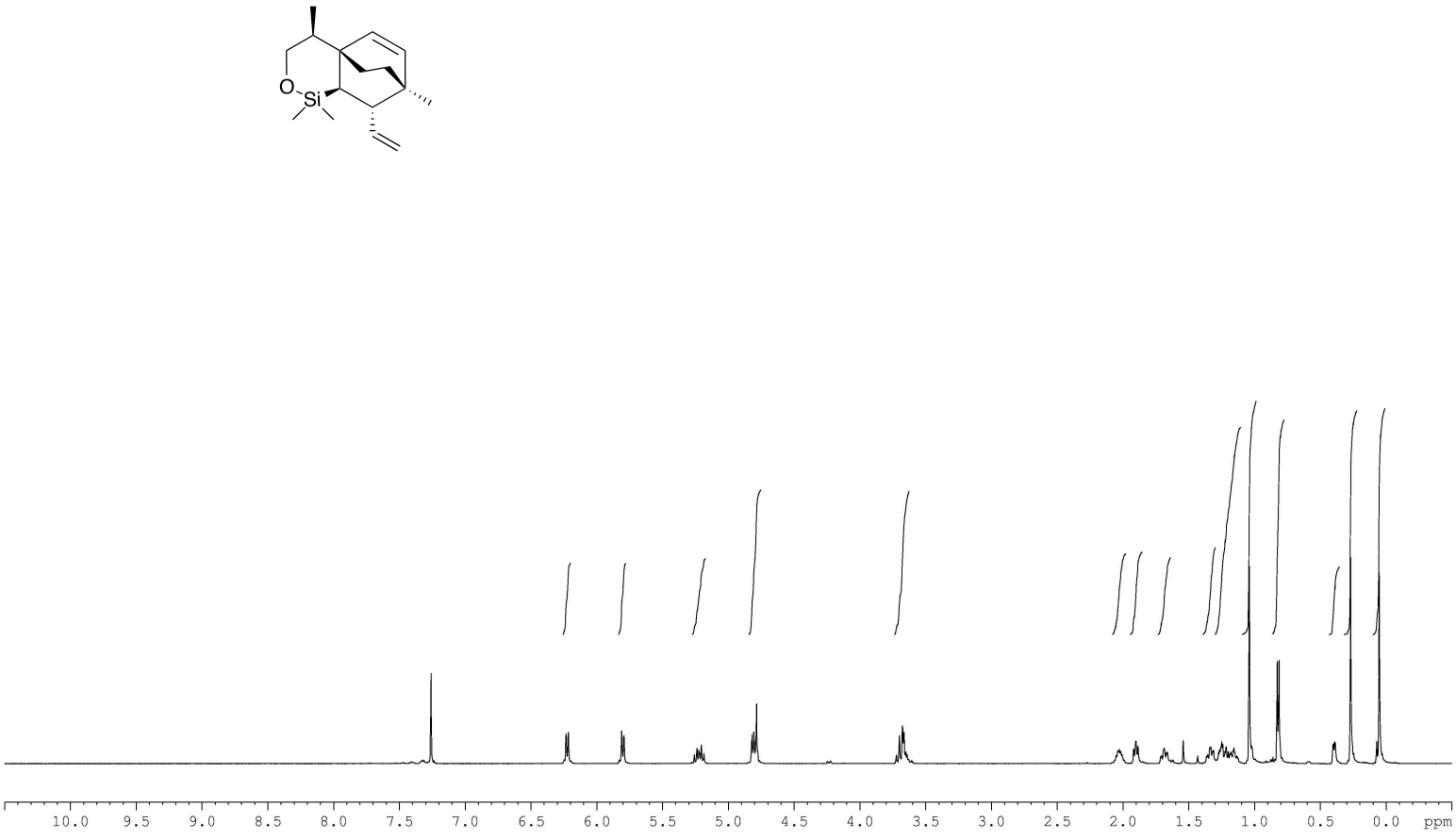



**Figure A1-35:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.23** in $CDCl_3$

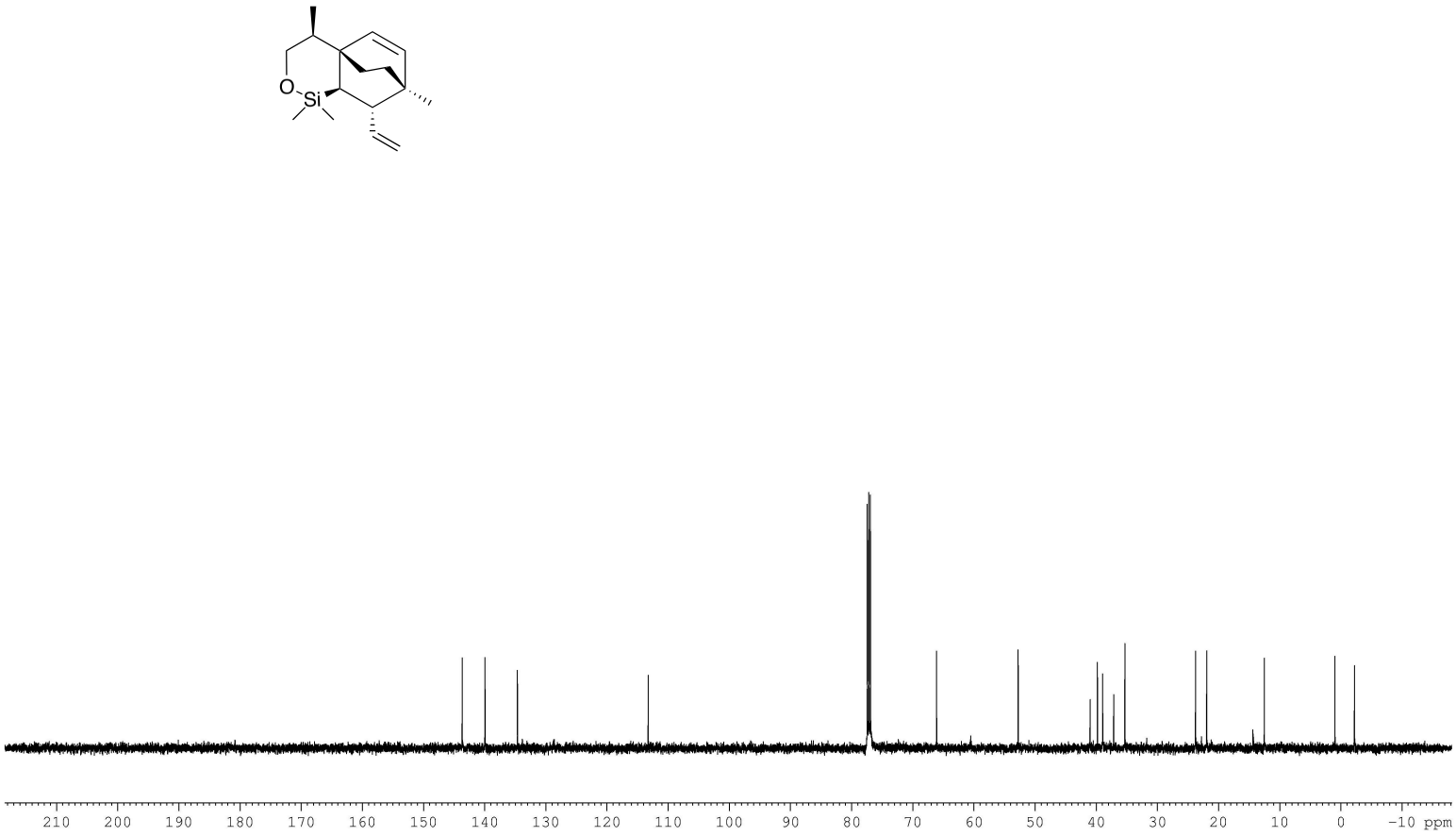



**Figure A1-36:** The 125 MHz $^{13}C$ NMR Spectrum of (–)-**2.23** in $CDCl_3$

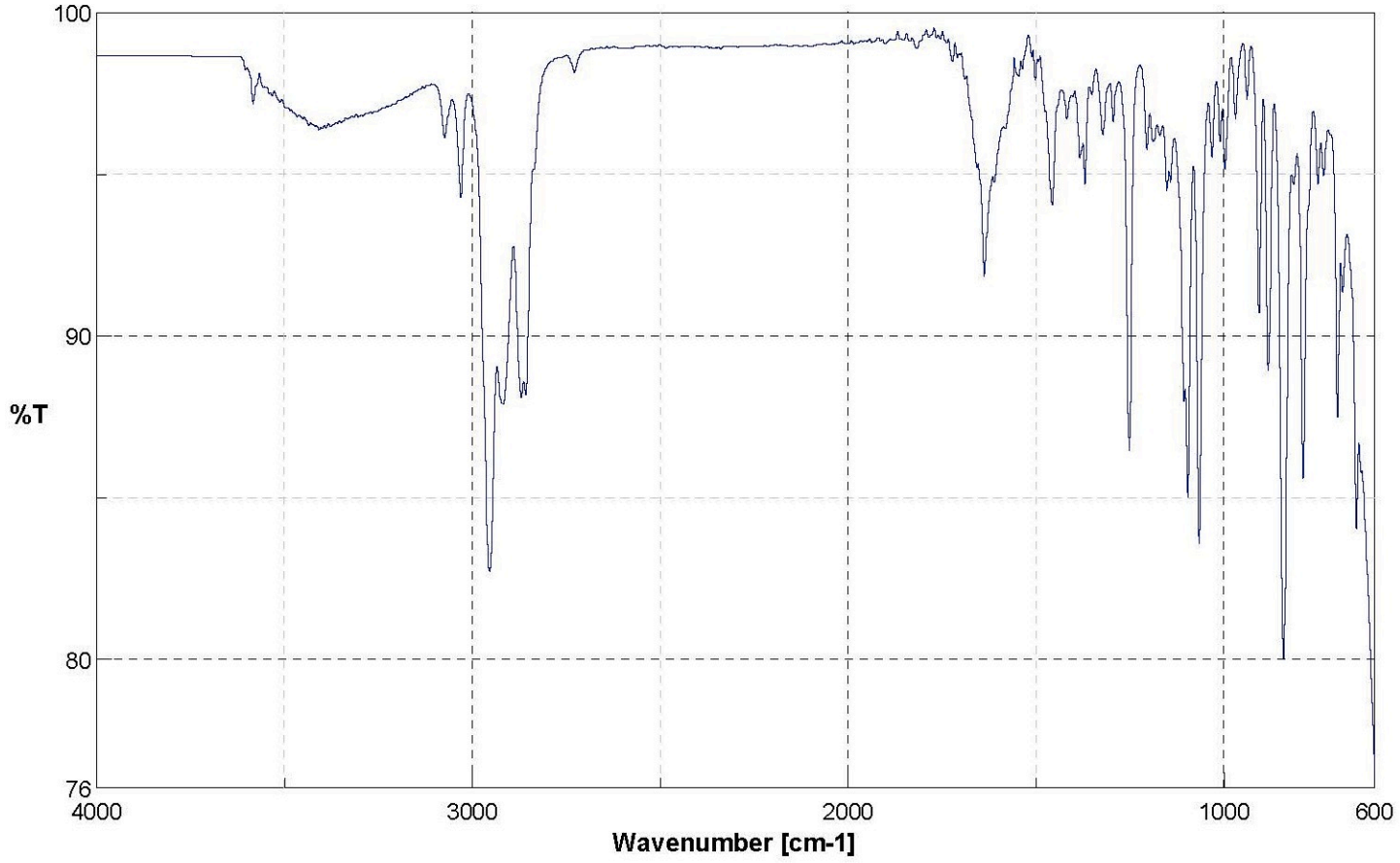



**Figure A1-37:** The Infrared Spectrum of Compound (–)-**2.23**

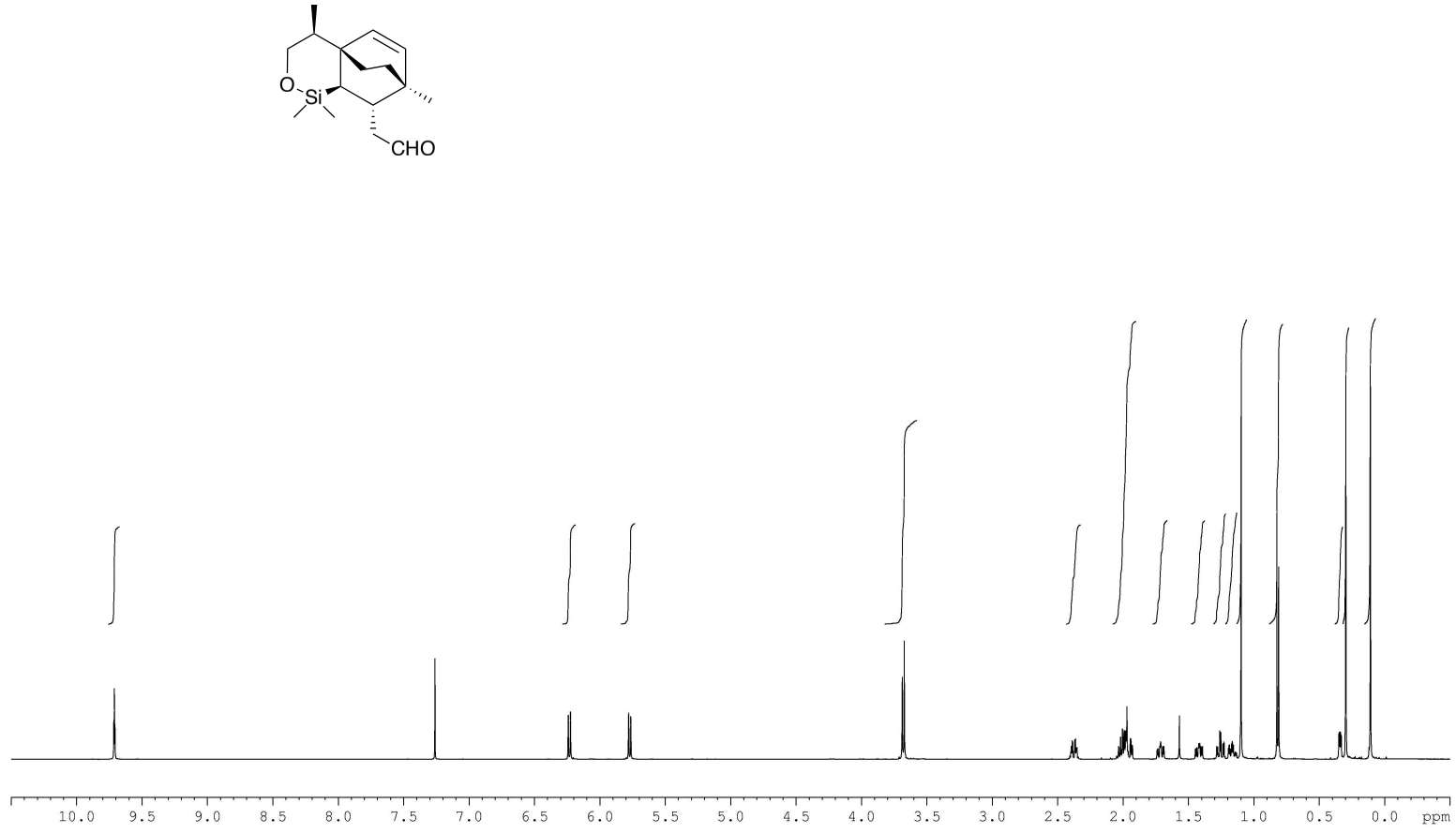



**Figure A1-38:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.28** in $CDCl_3$

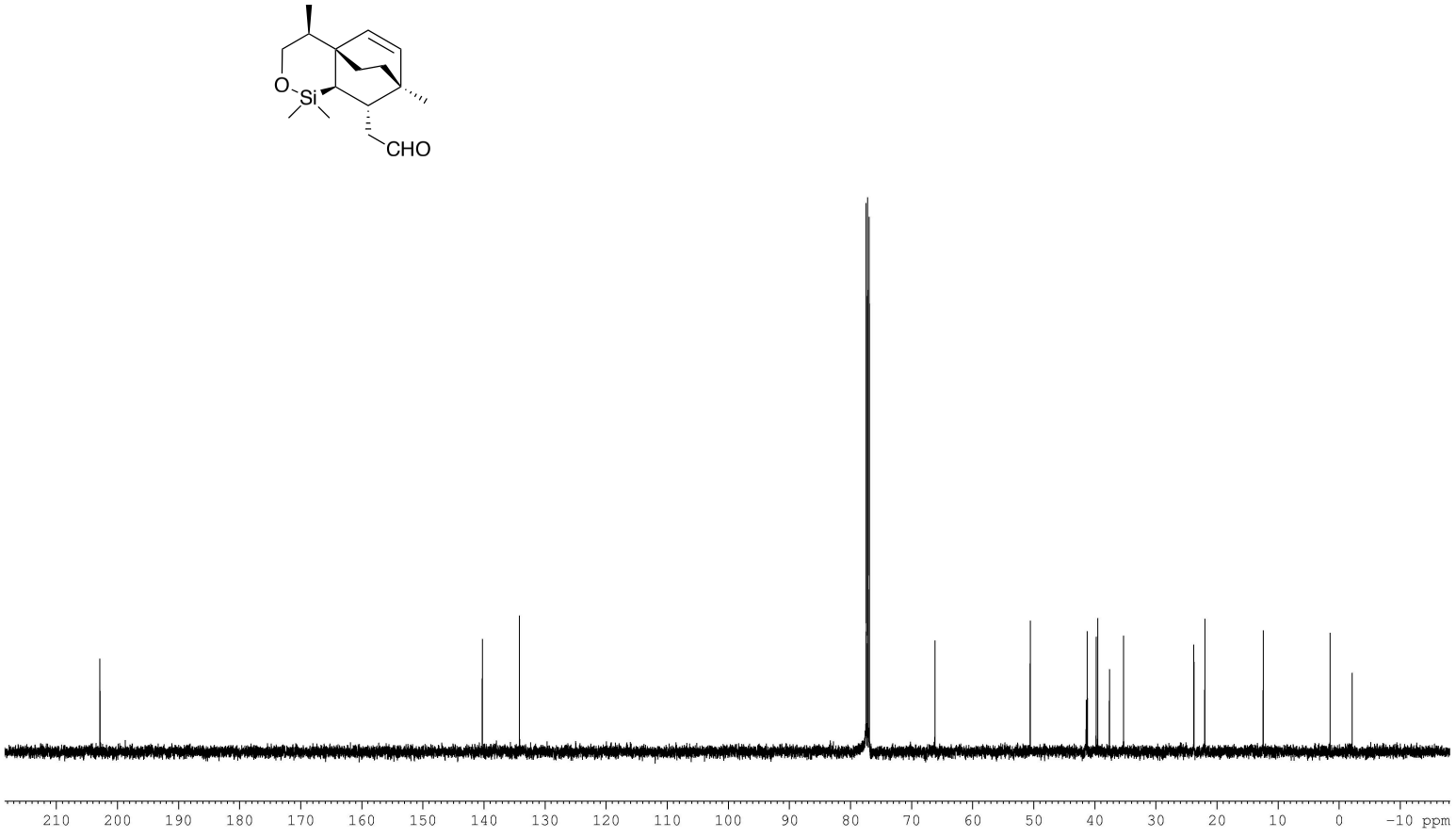



**Figure A1-39:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.28** in $CDCl_3$

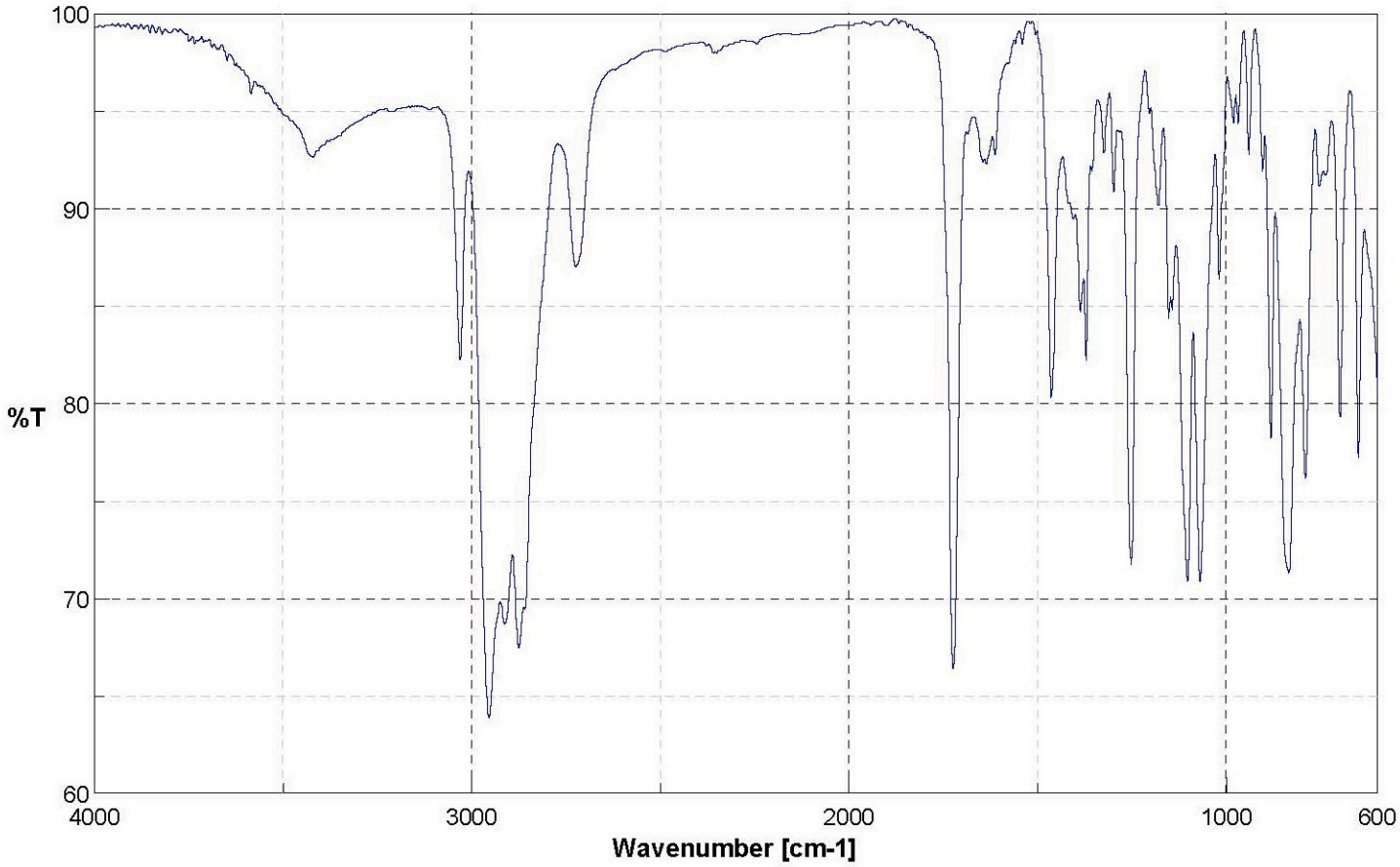



**Figure A1-40:** The Infrared Spectrum of Compound (–)-**2.28**

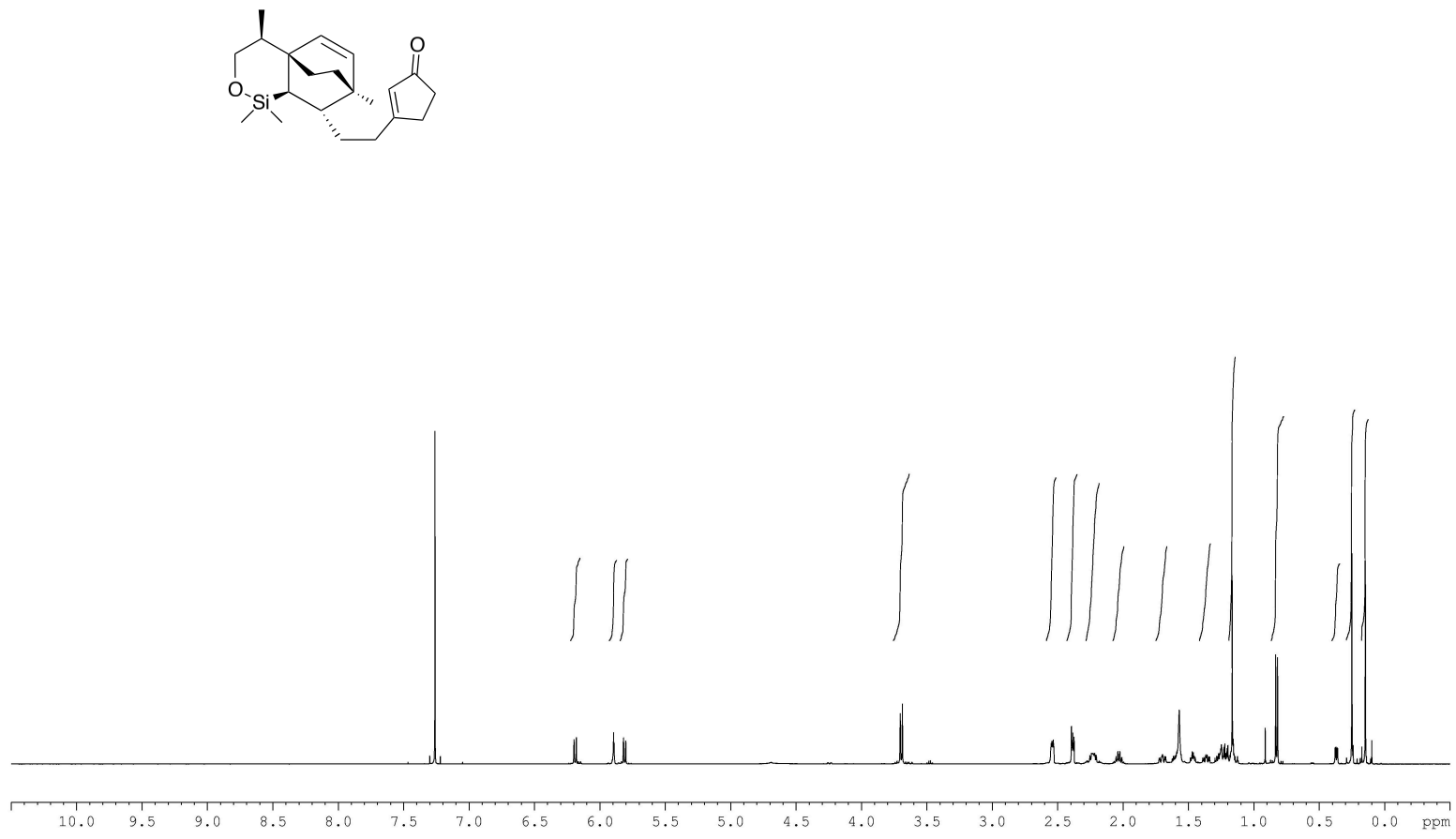



**Figure A1-41:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.20** in $CDCl_3$

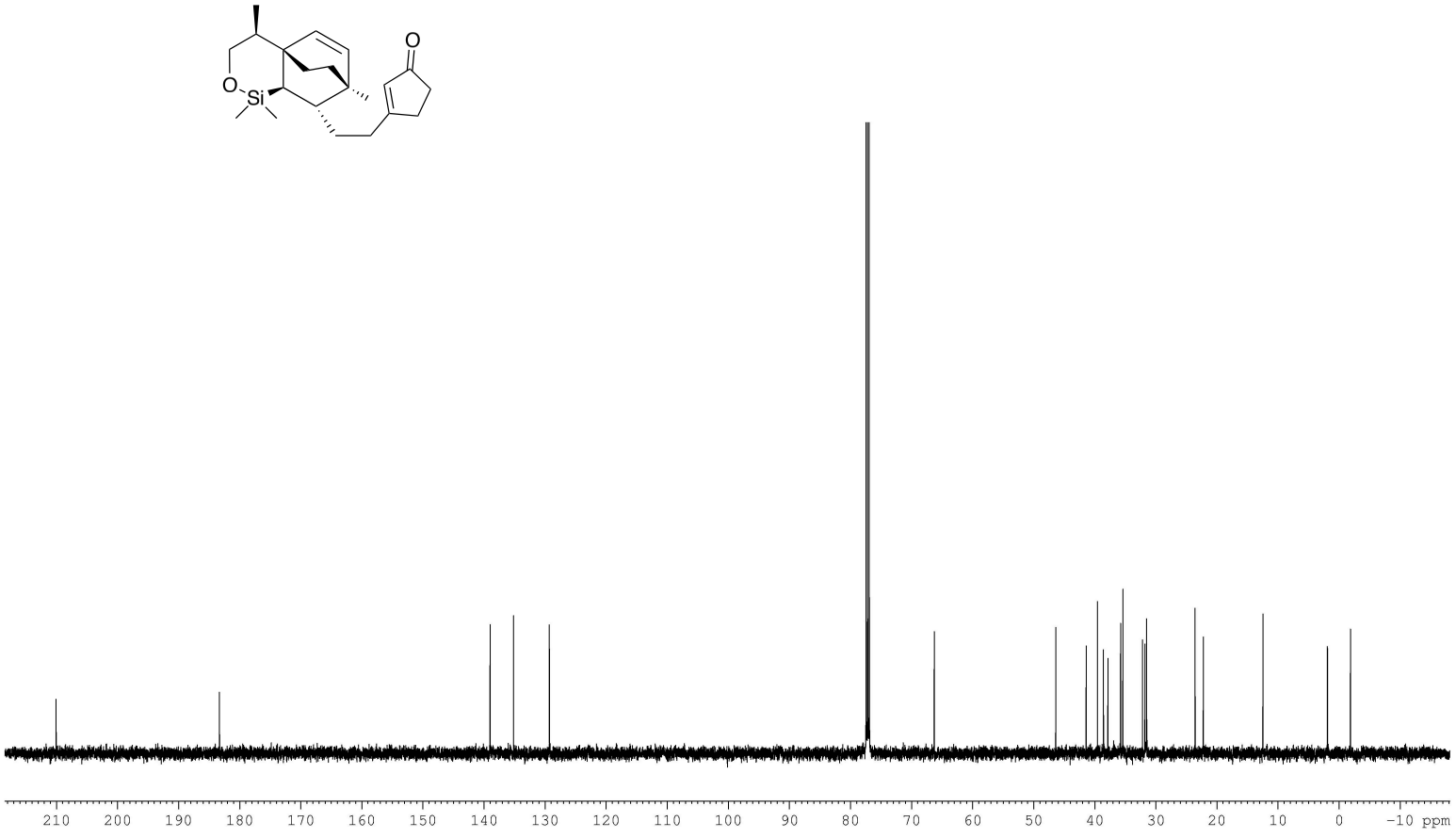



**Figure A1-42:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.20** in $CDCl_3$

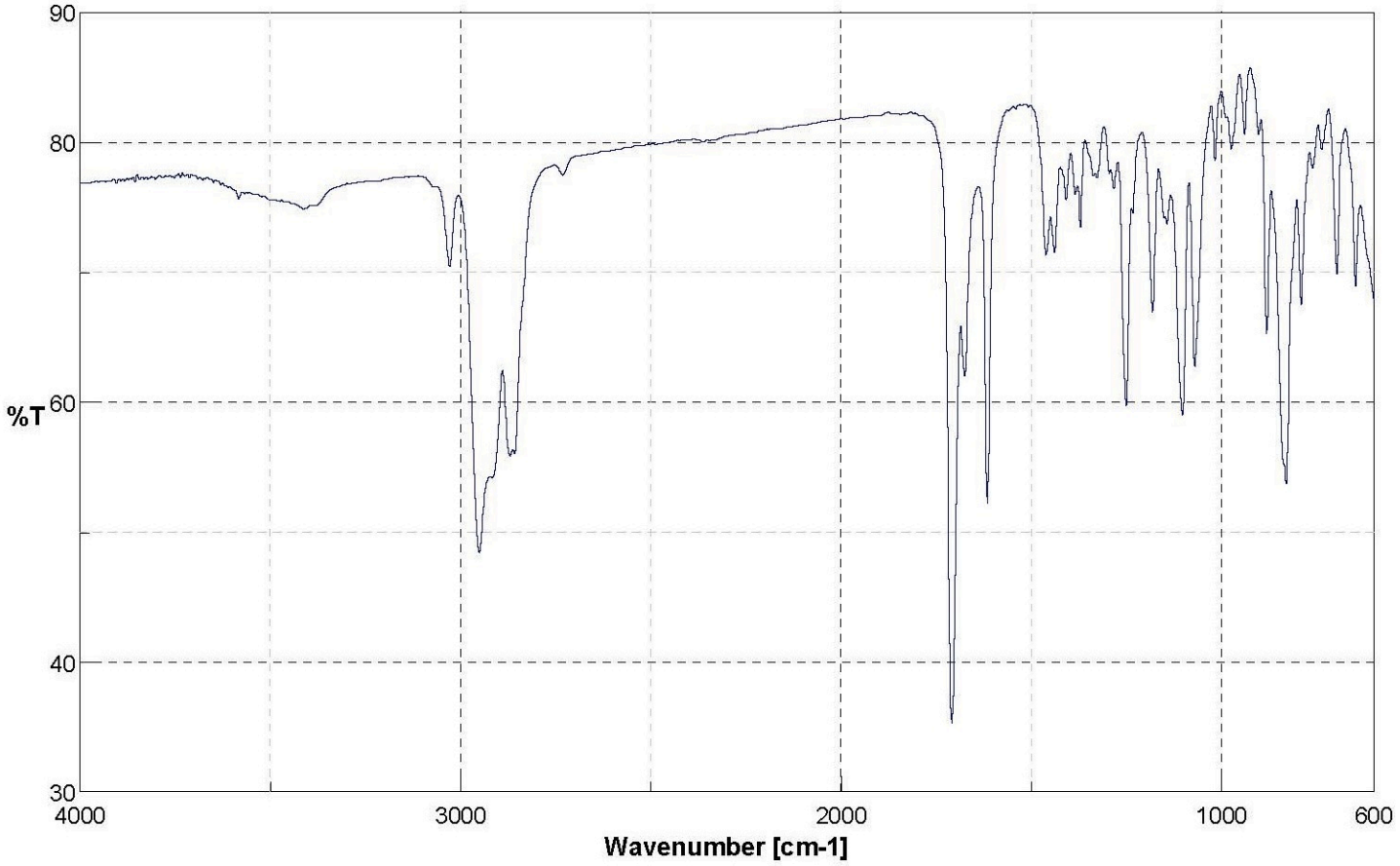



**Figure A1-43:** The Infrared Spectrum of Compound (–)-**2.20**

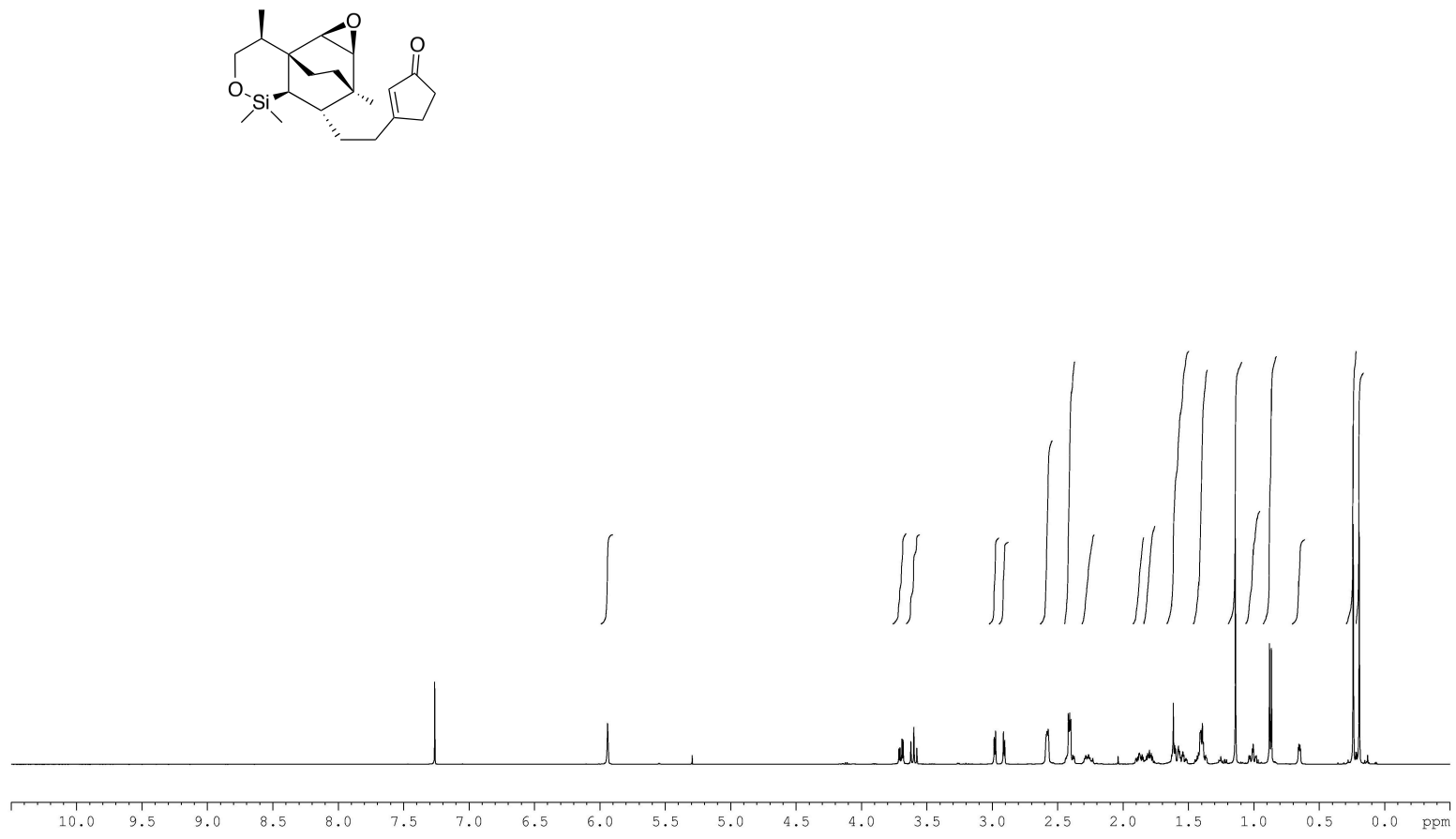



**Figure A1-44:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.29** in $CDCl_3$

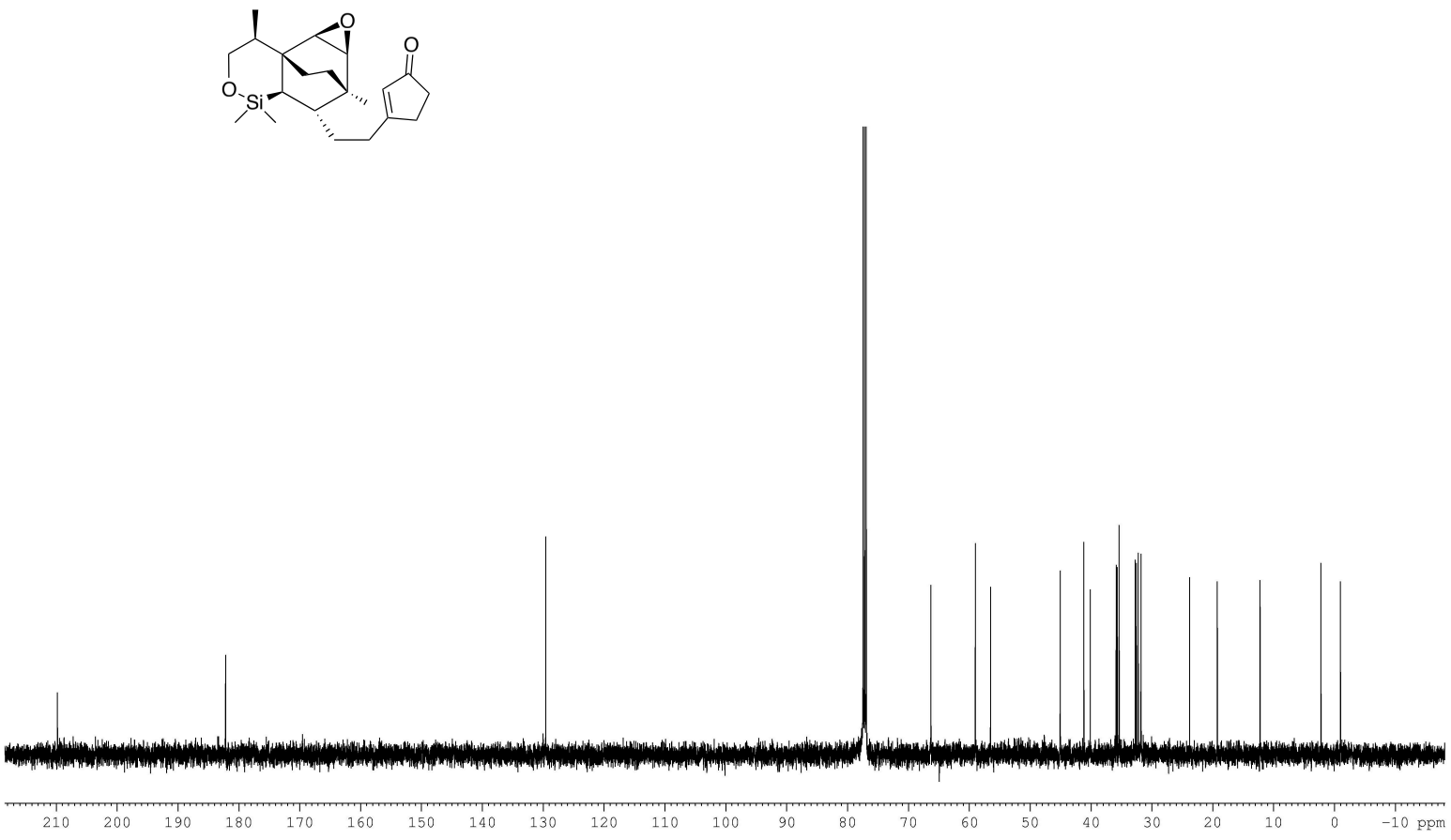



**Figure A1-45:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.29** in $CDCl_3$

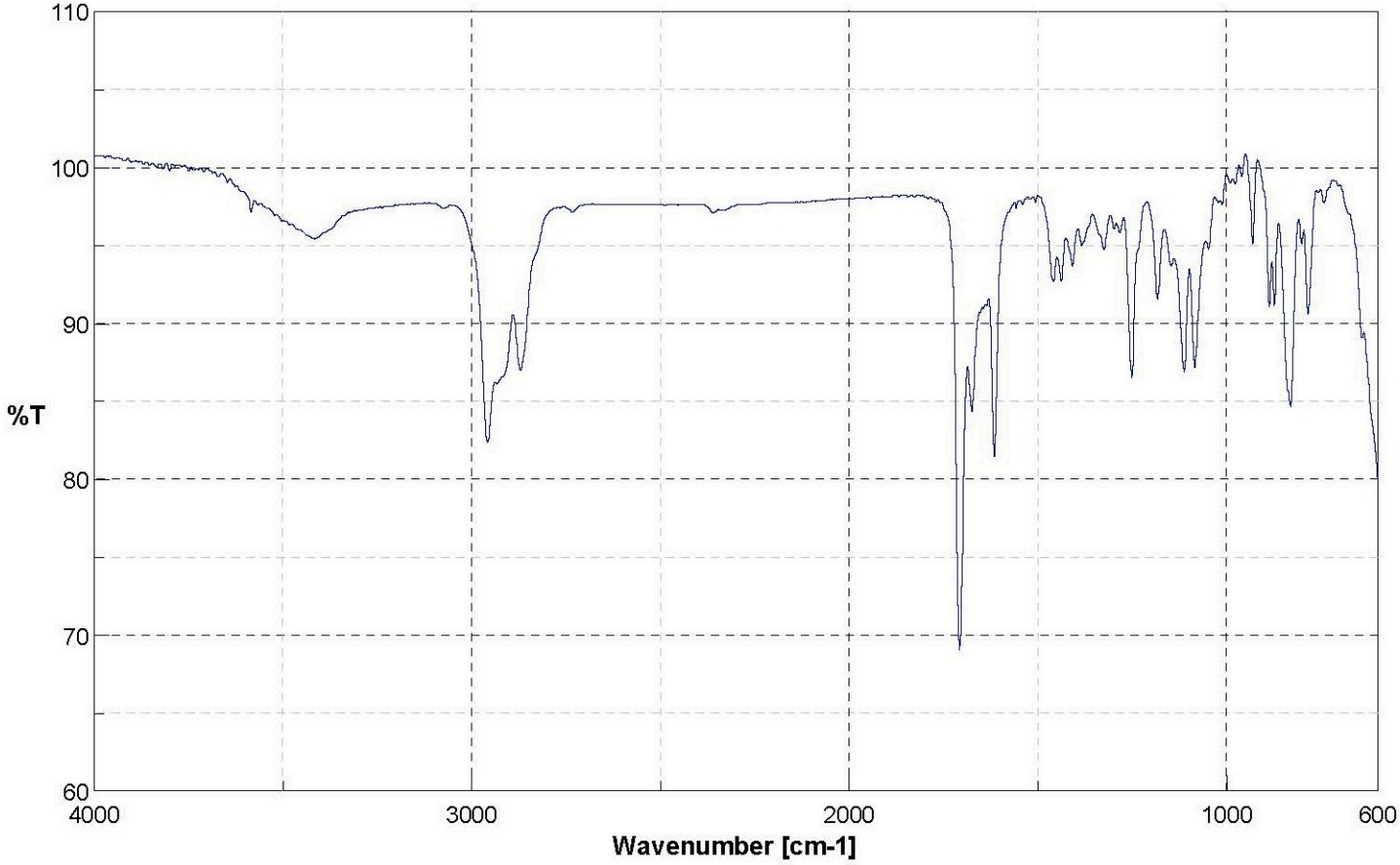



**Figure A1-46:** The Infrared Spectrum of Compound (–)-**2.29**

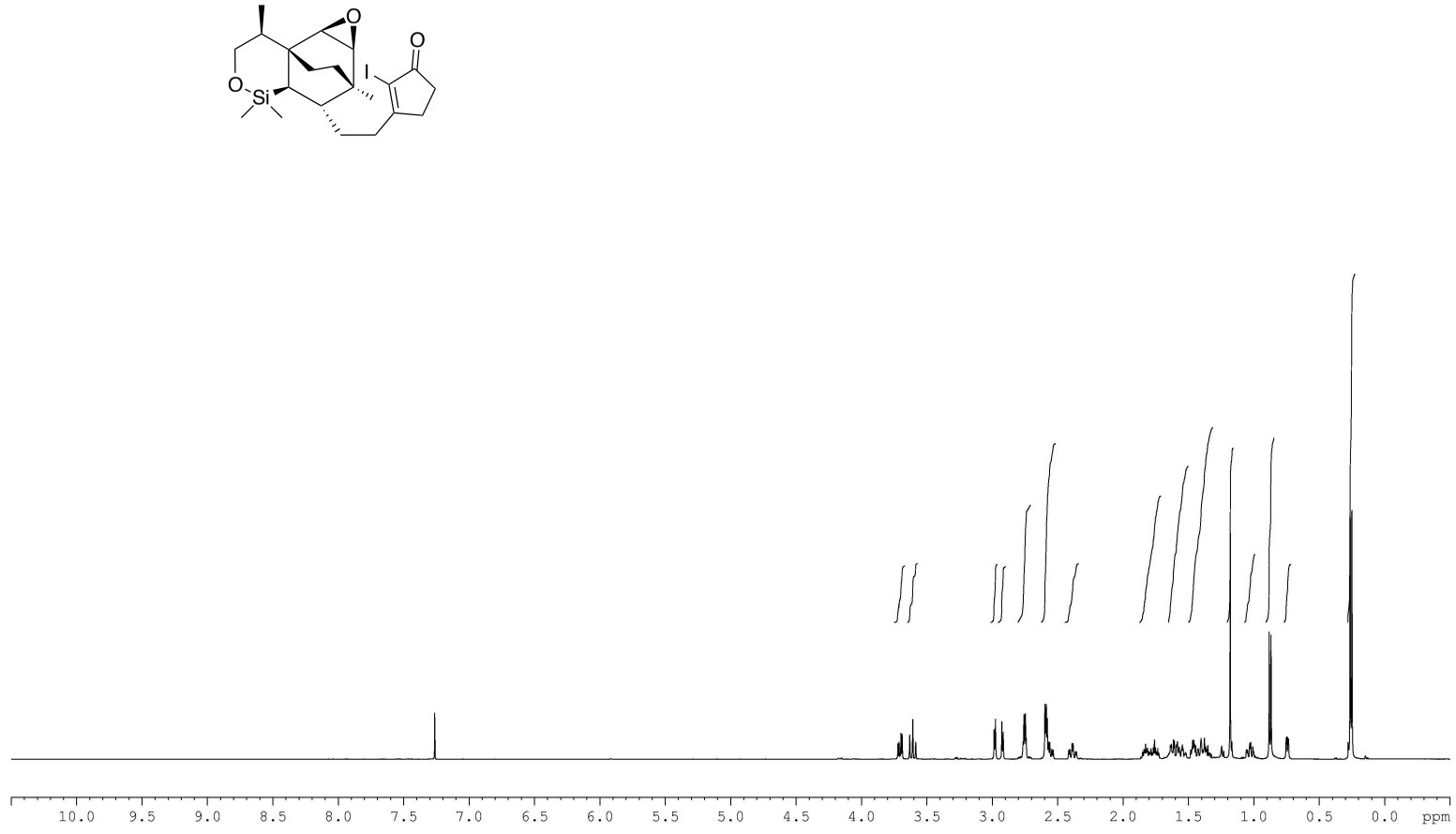



**Figure A1-47:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**2.3** in $CDCl_3$

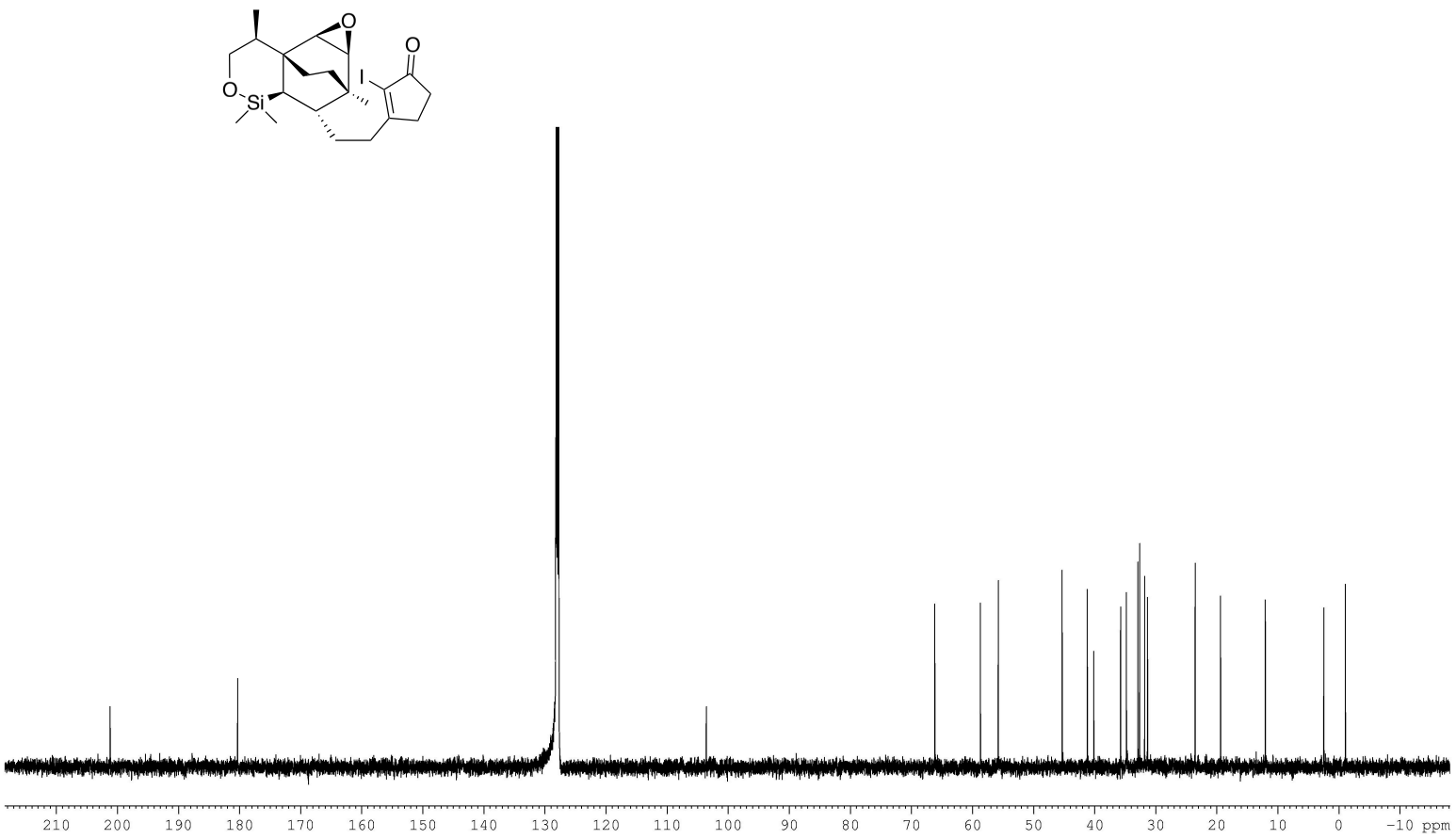



**Figure A1-48:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**2.3** in $C_6D_6$

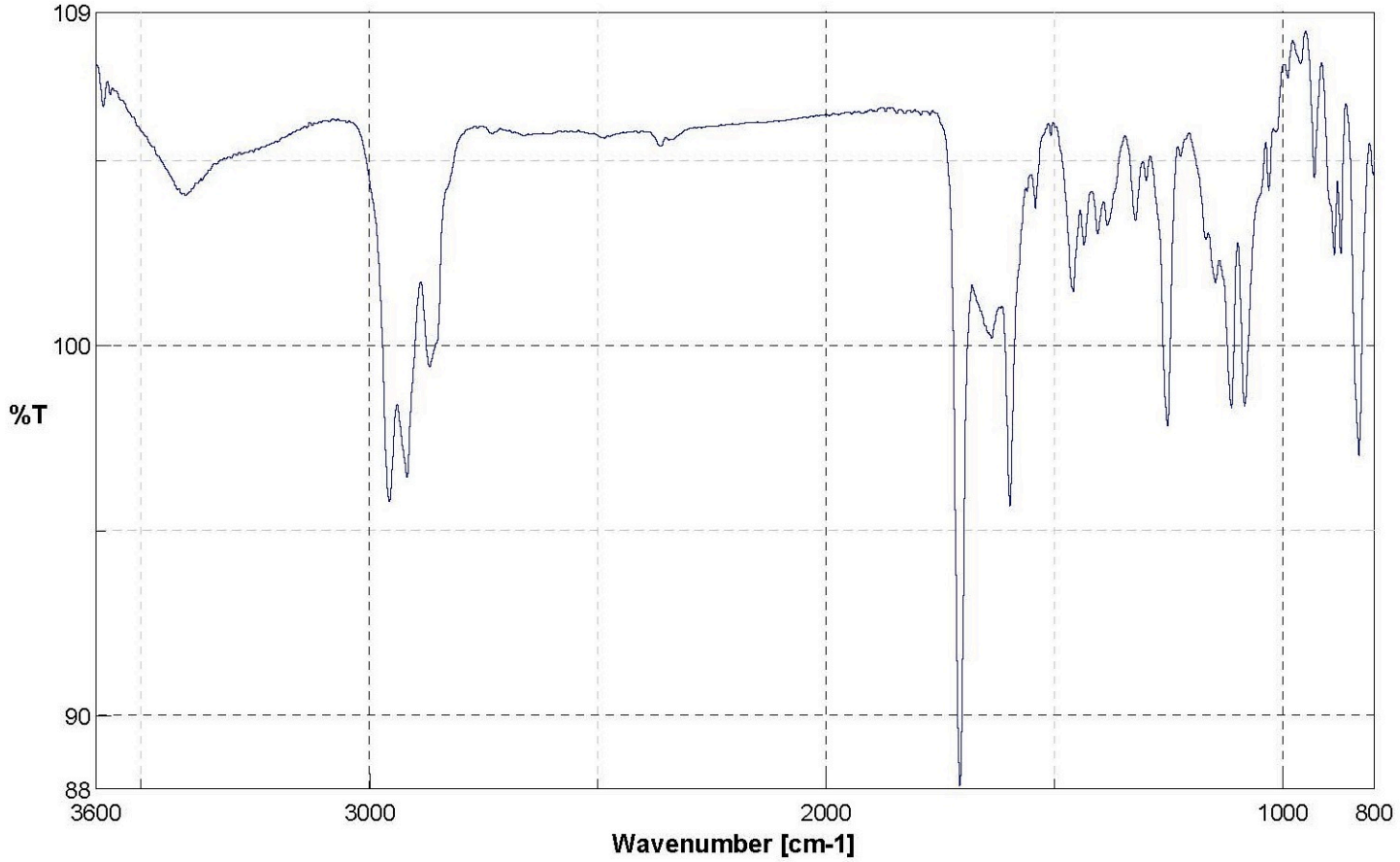



**Figure A1-49:** The Infrared Spectrum of Compound (+)-**2.3**

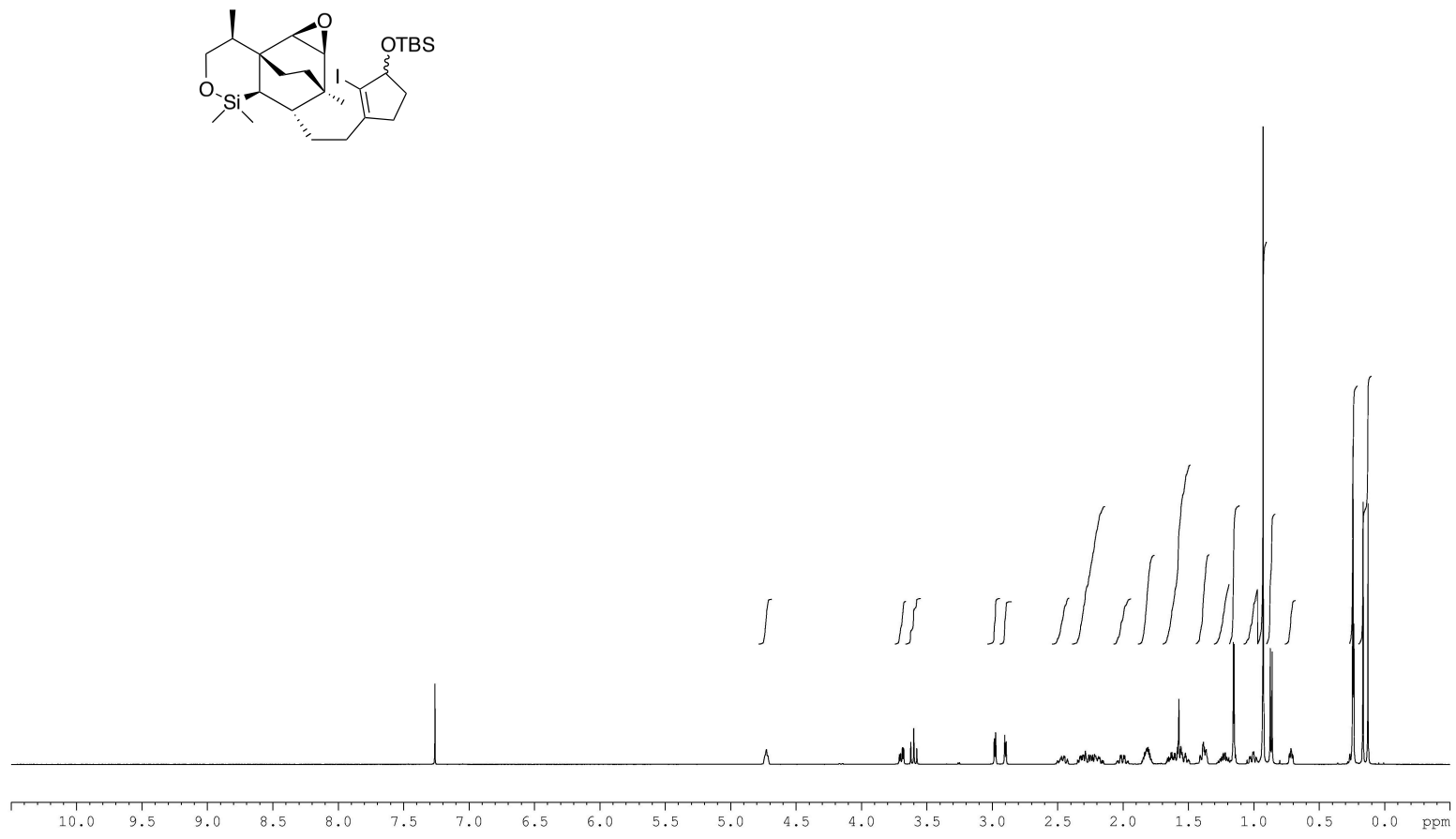



**Figure A1-50:** The 500 MHz $^{1}$H NMR Spectrum of Compound **2.30** in $CDCl_3$

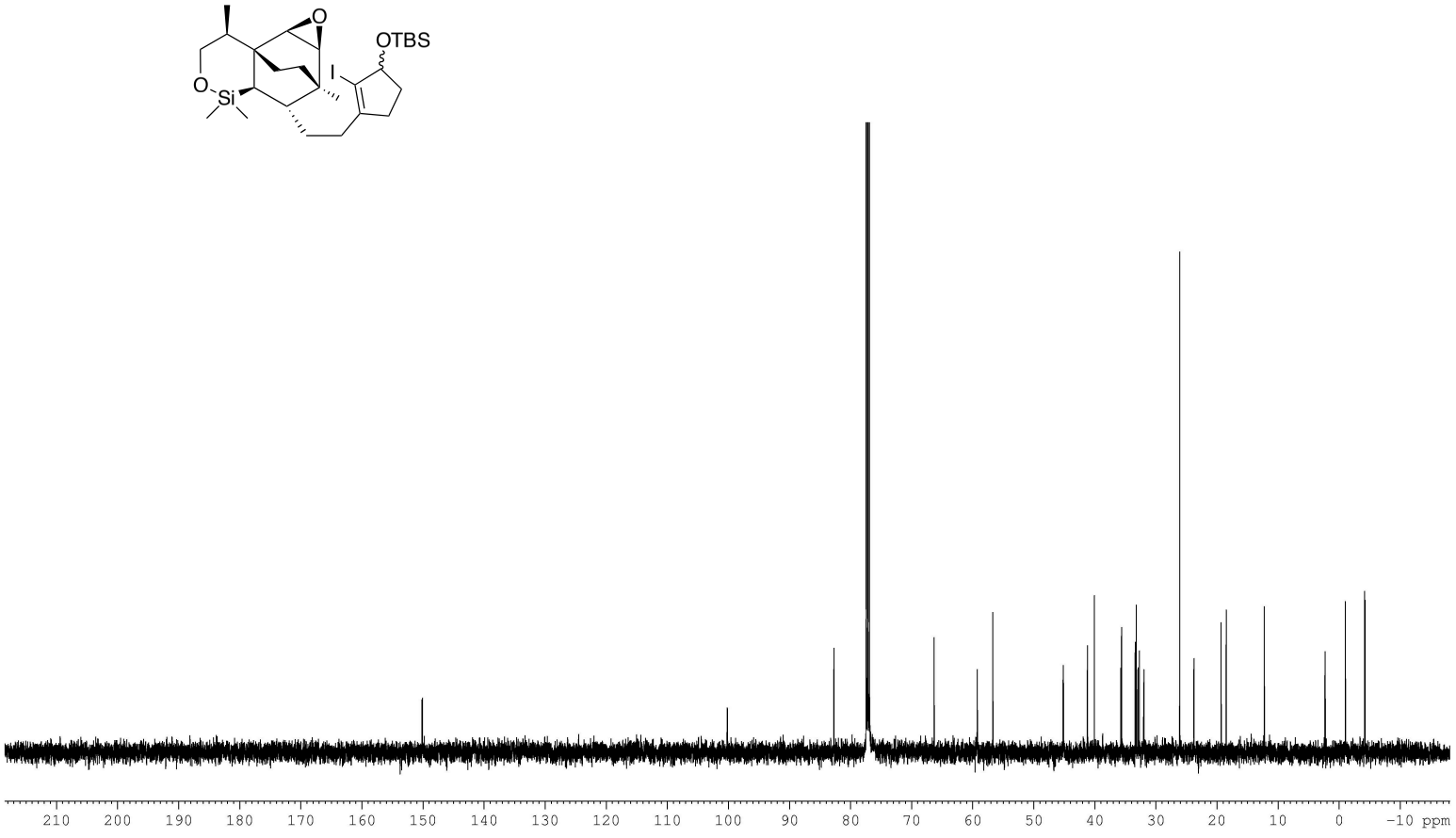



**Figure A1-51:** The 125 MHz $^{13}C$ NMR Spectrum of Compound **2.30** in $CDCl_3$

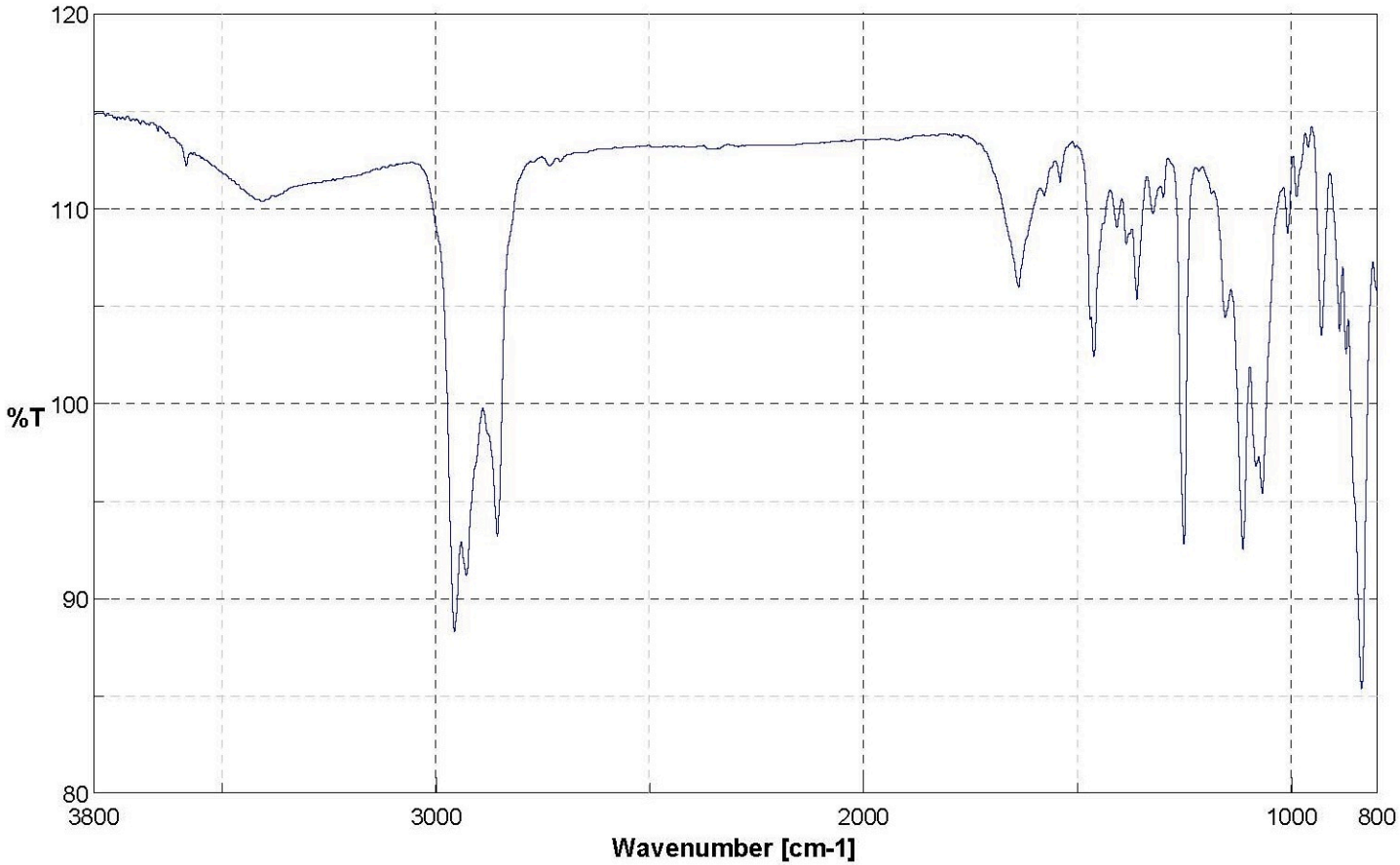



**Figure A1-52:** The Infrared Spectrum of Compound **2.30**

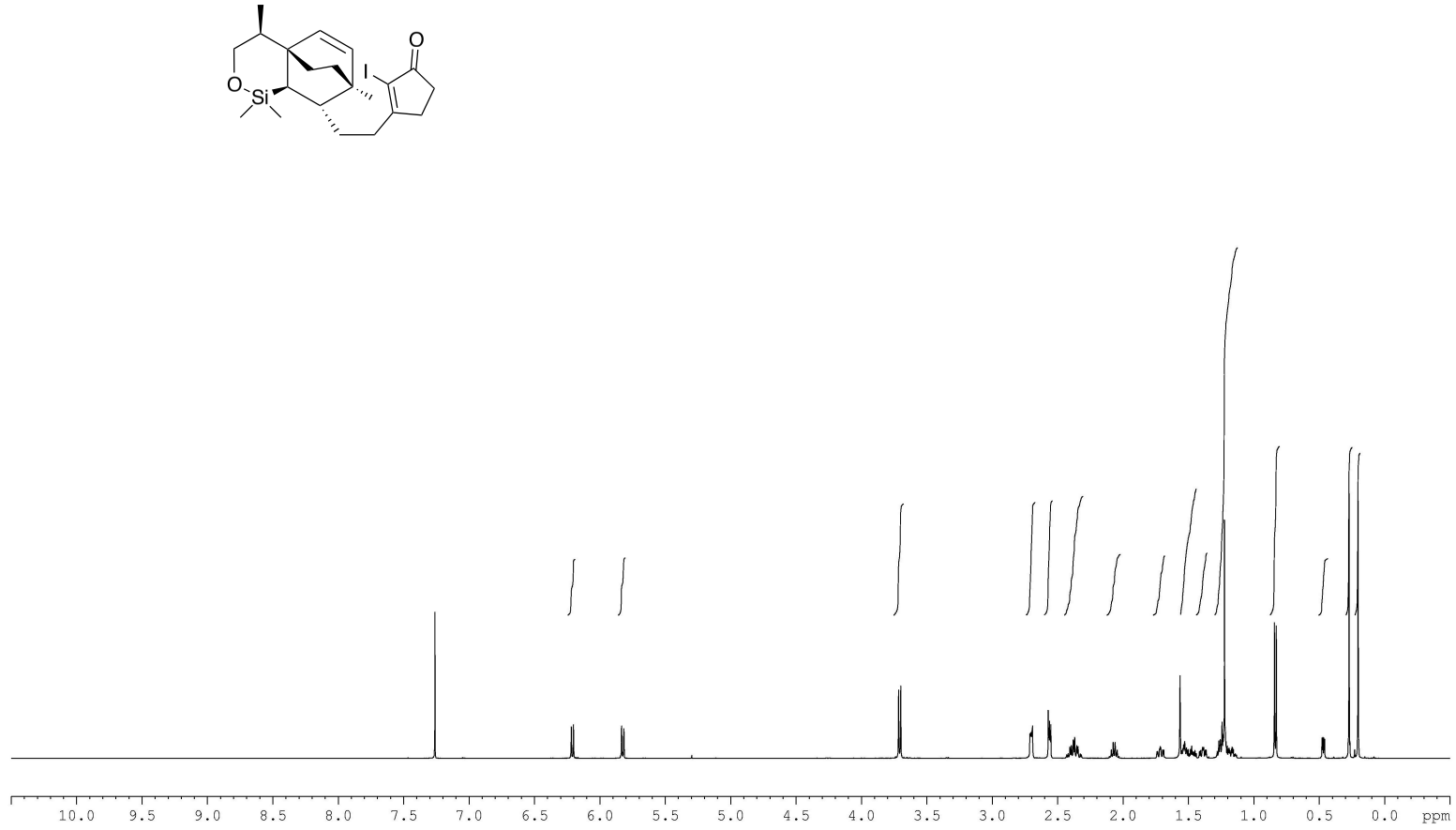



**Figure A1-53:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.37** in $CDCl_3$

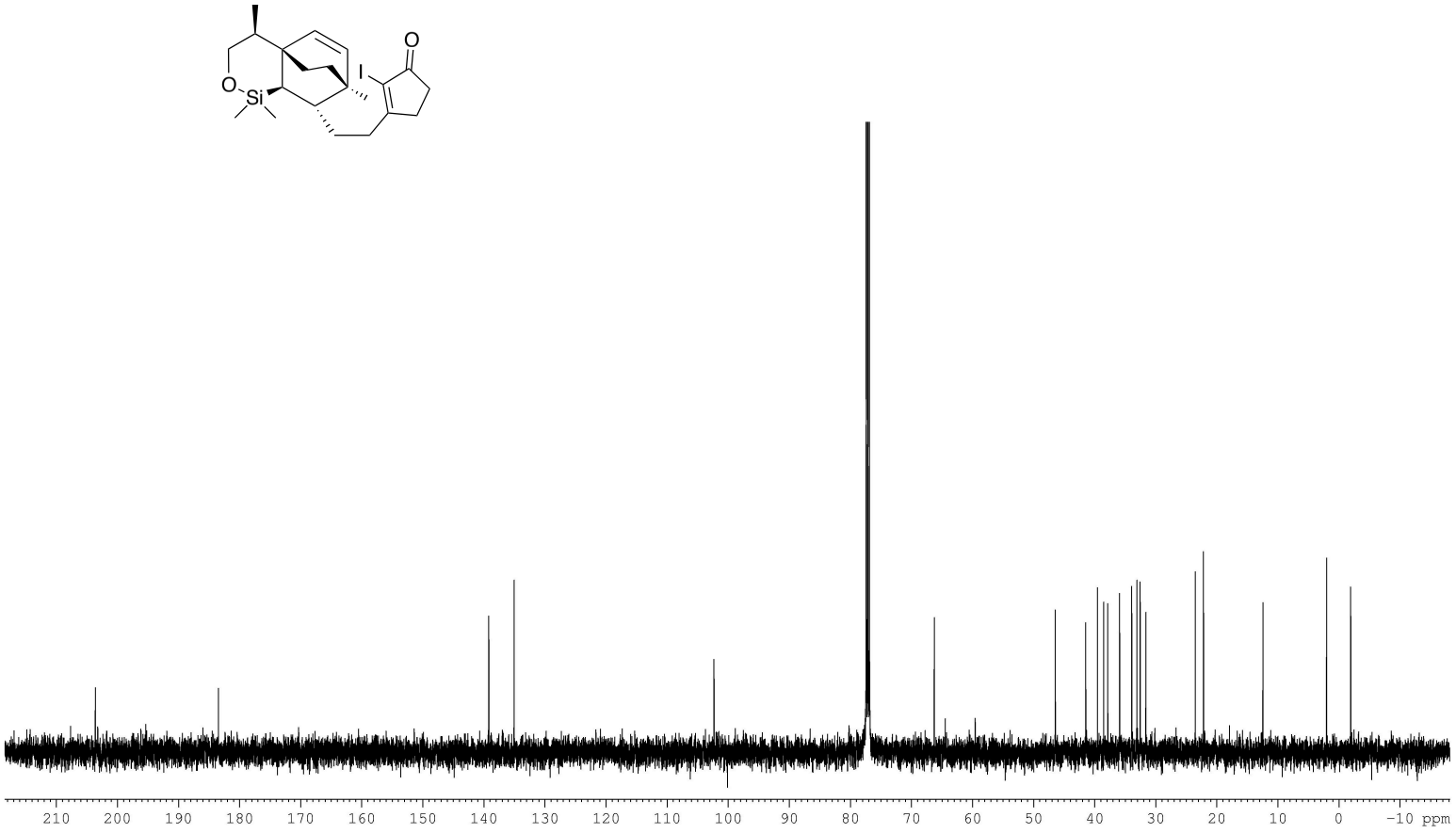



**Figure A1-54:** The 125 MHz $^{13}C$ NMR Spectrum of (–)-**2.37** in $CDCl_3$

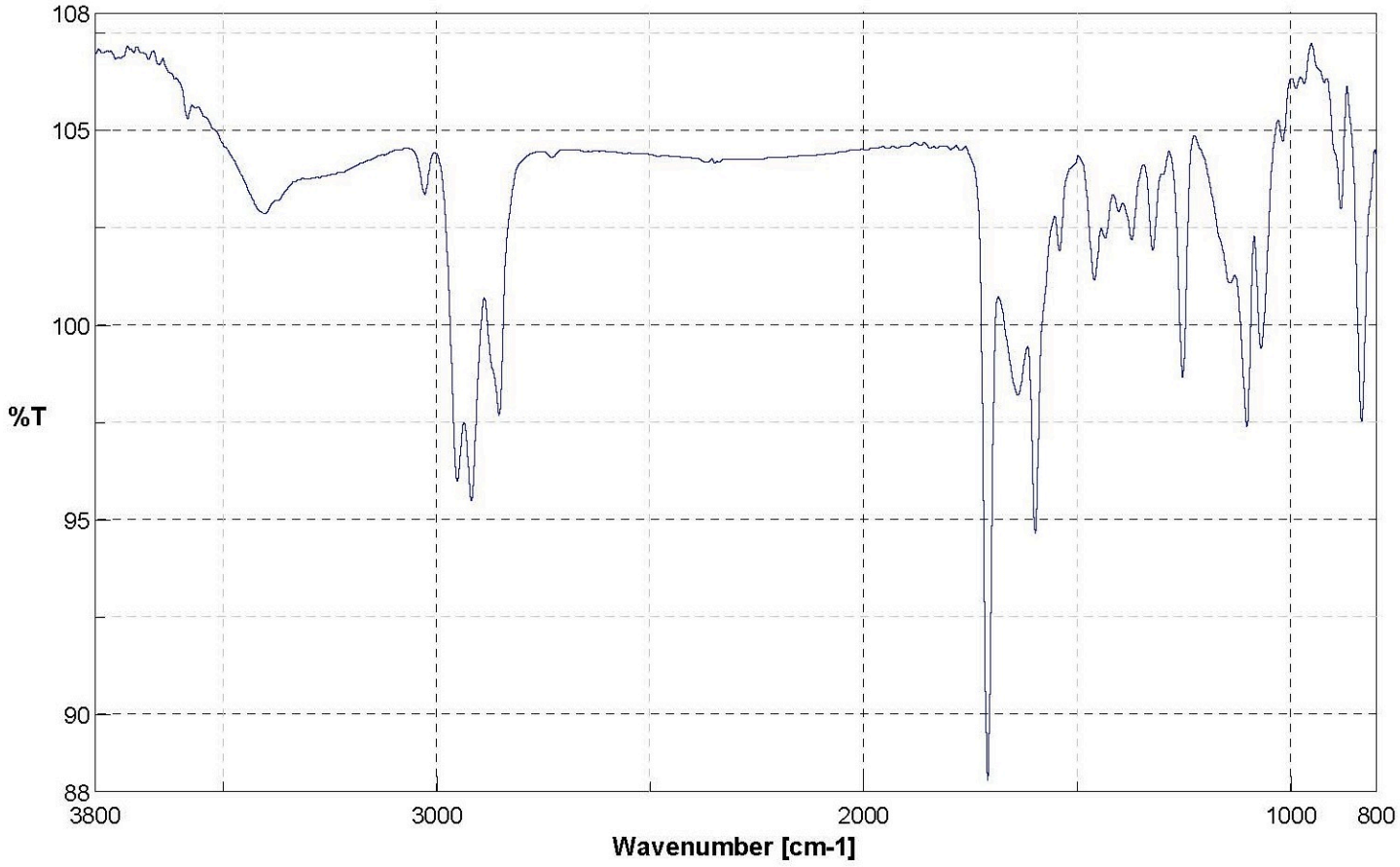



**Figure A1-55:** The Infrared Spectrum of Compound (–)-**2.37**

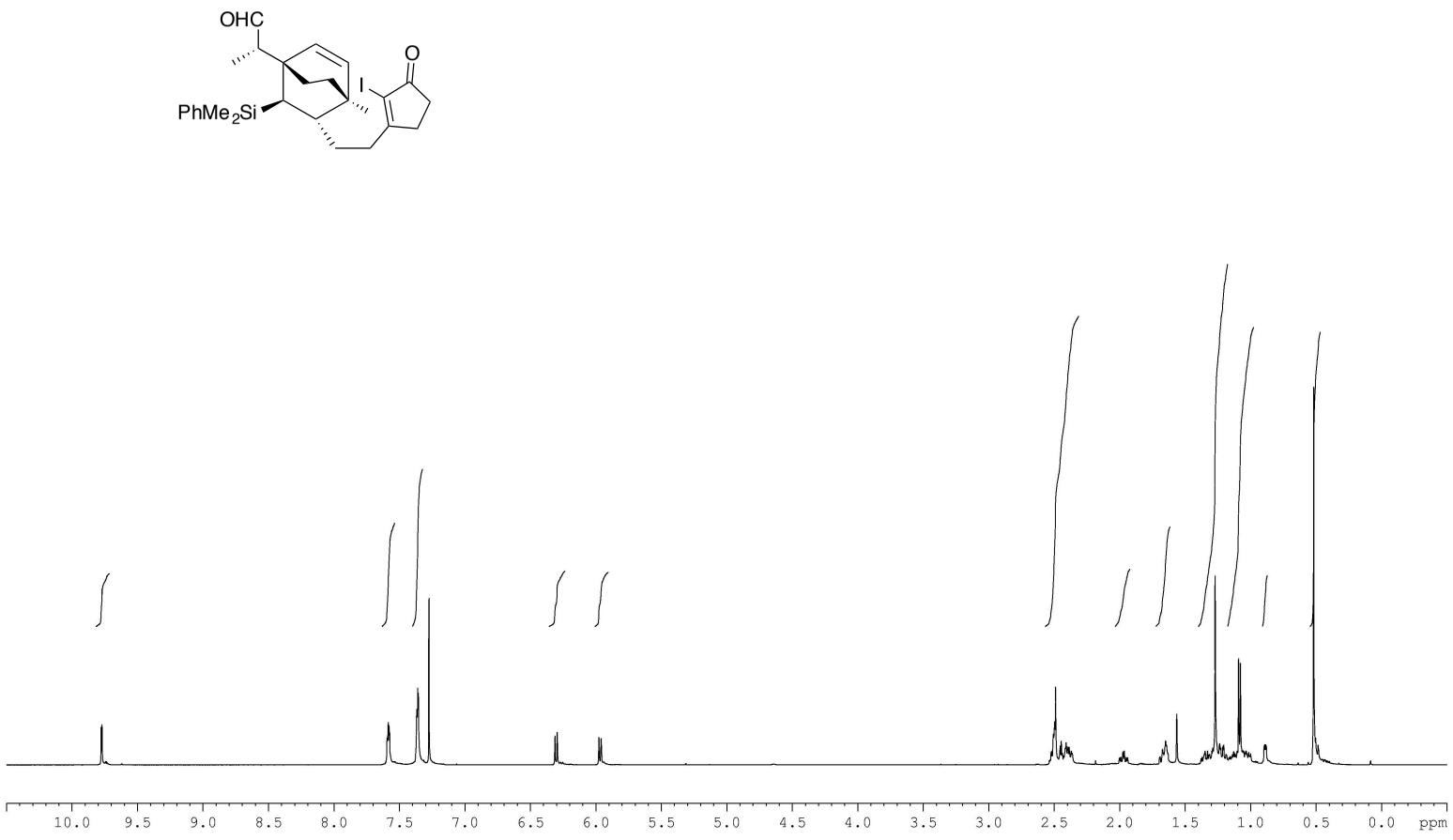



**Figure A1-56:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.39** in $CDCl_3$

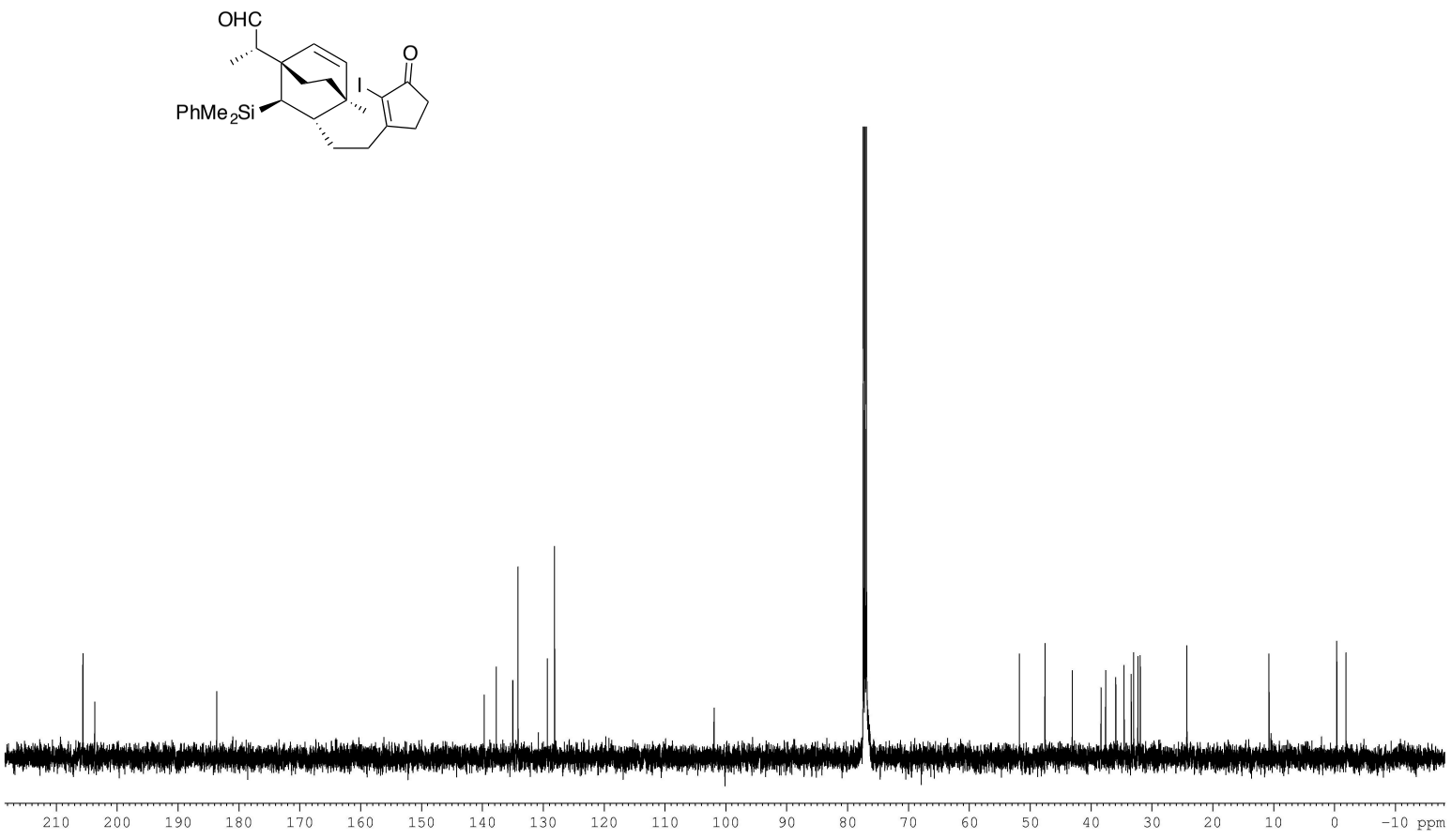



**Figure A1-57:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.39** in $CDCl_3$

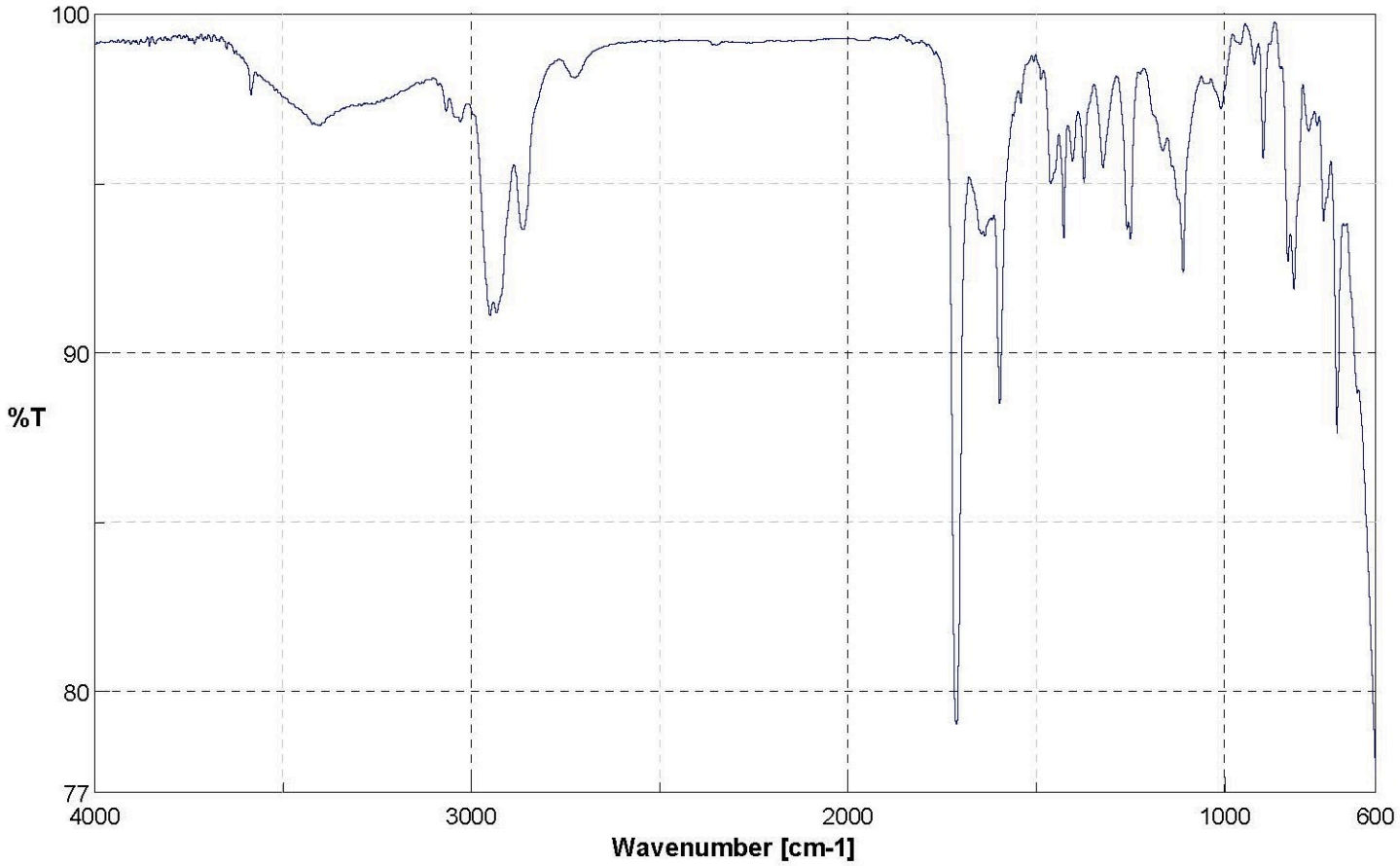



**Figure A1-58:** The Infrared Spectrum of Compound (–)-**2.39**

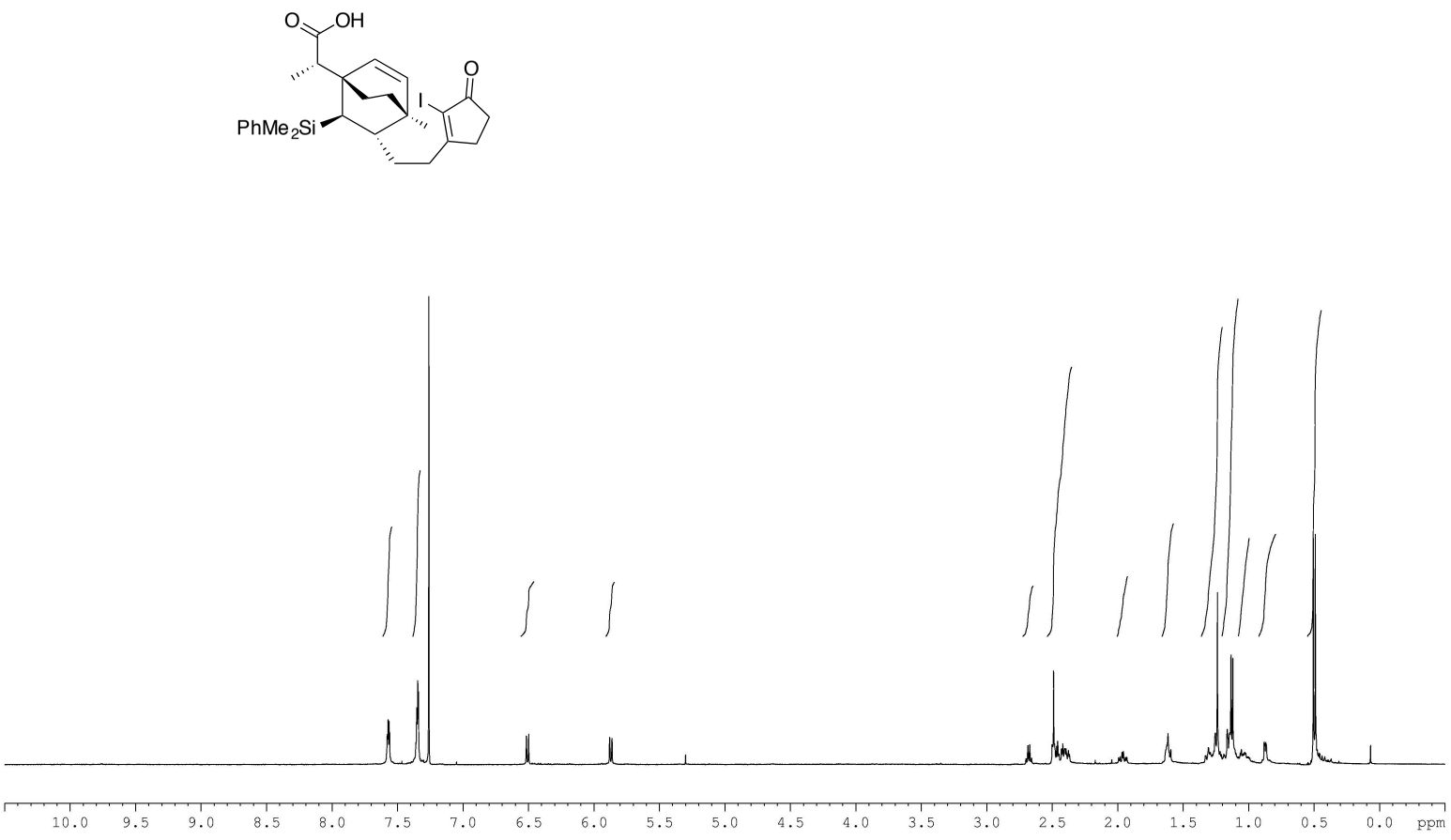



**Figure A1-59:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**2.32** in $CDCl_3$

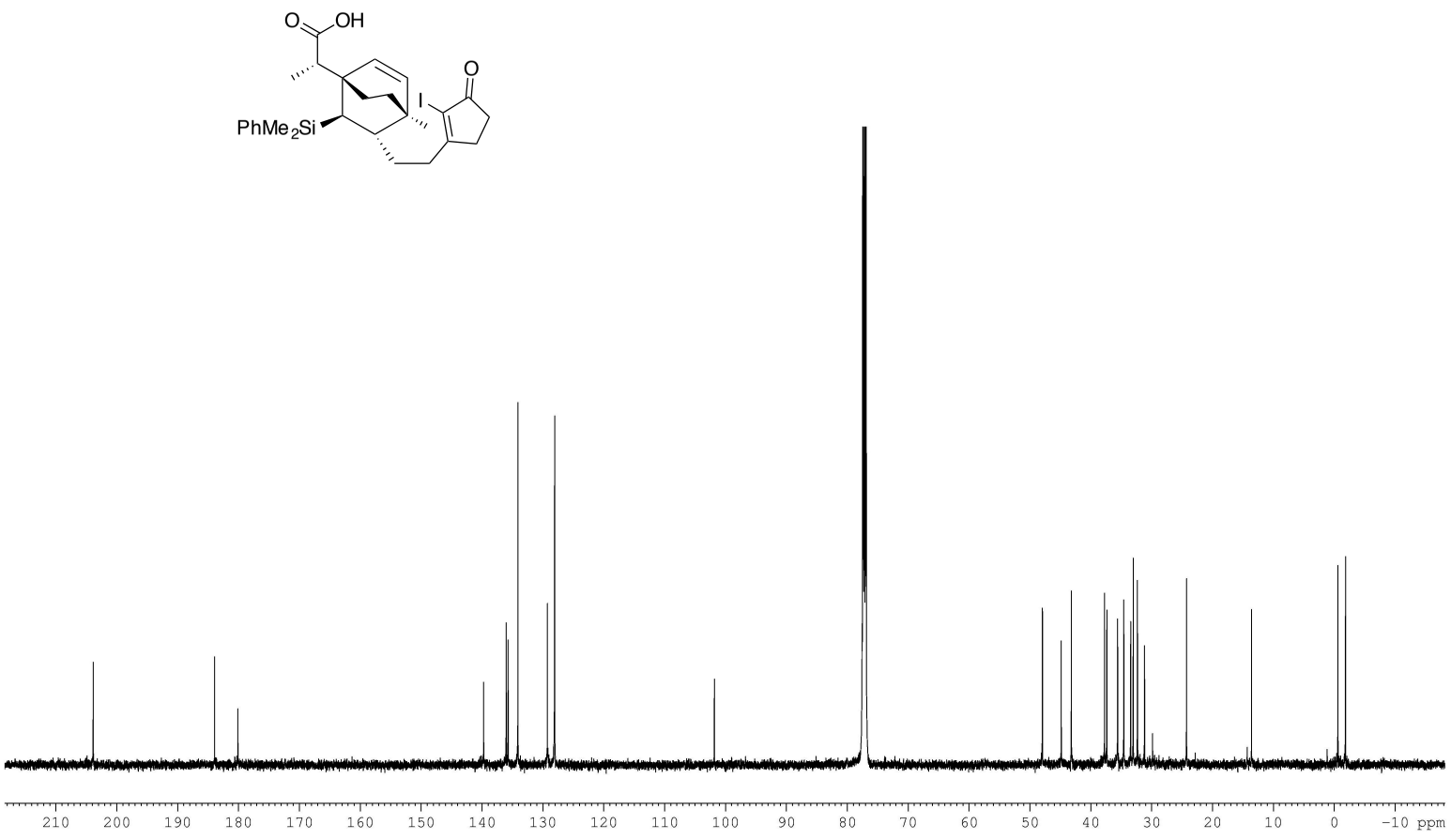



**Figure A1-60:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**2.32** in $CDCl_3$

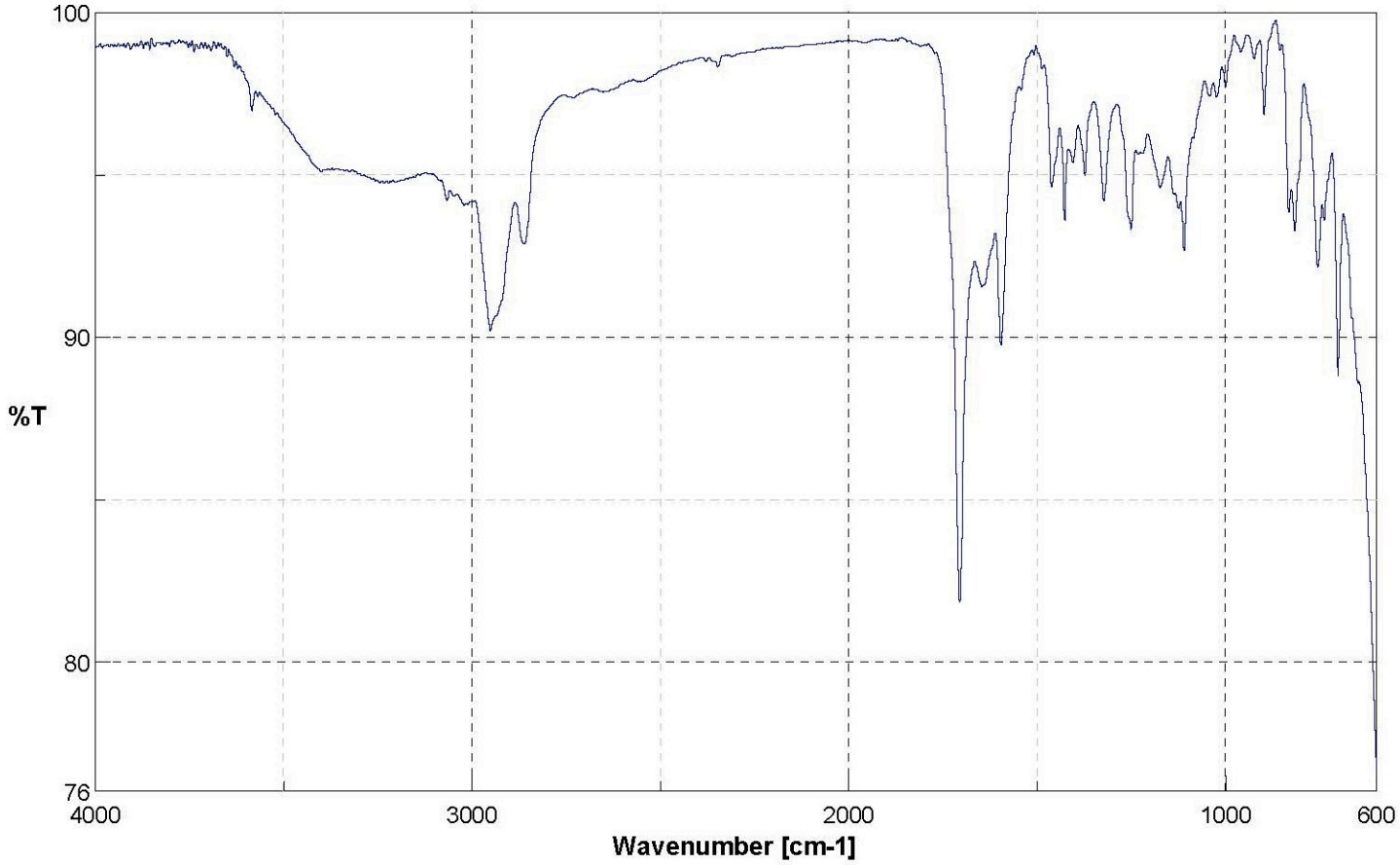



**Figure A1-61:** The Infrared Spectrum of Compound (–)-**2.32**

# Appendix 2: Spectra Relevant to Chapter 3

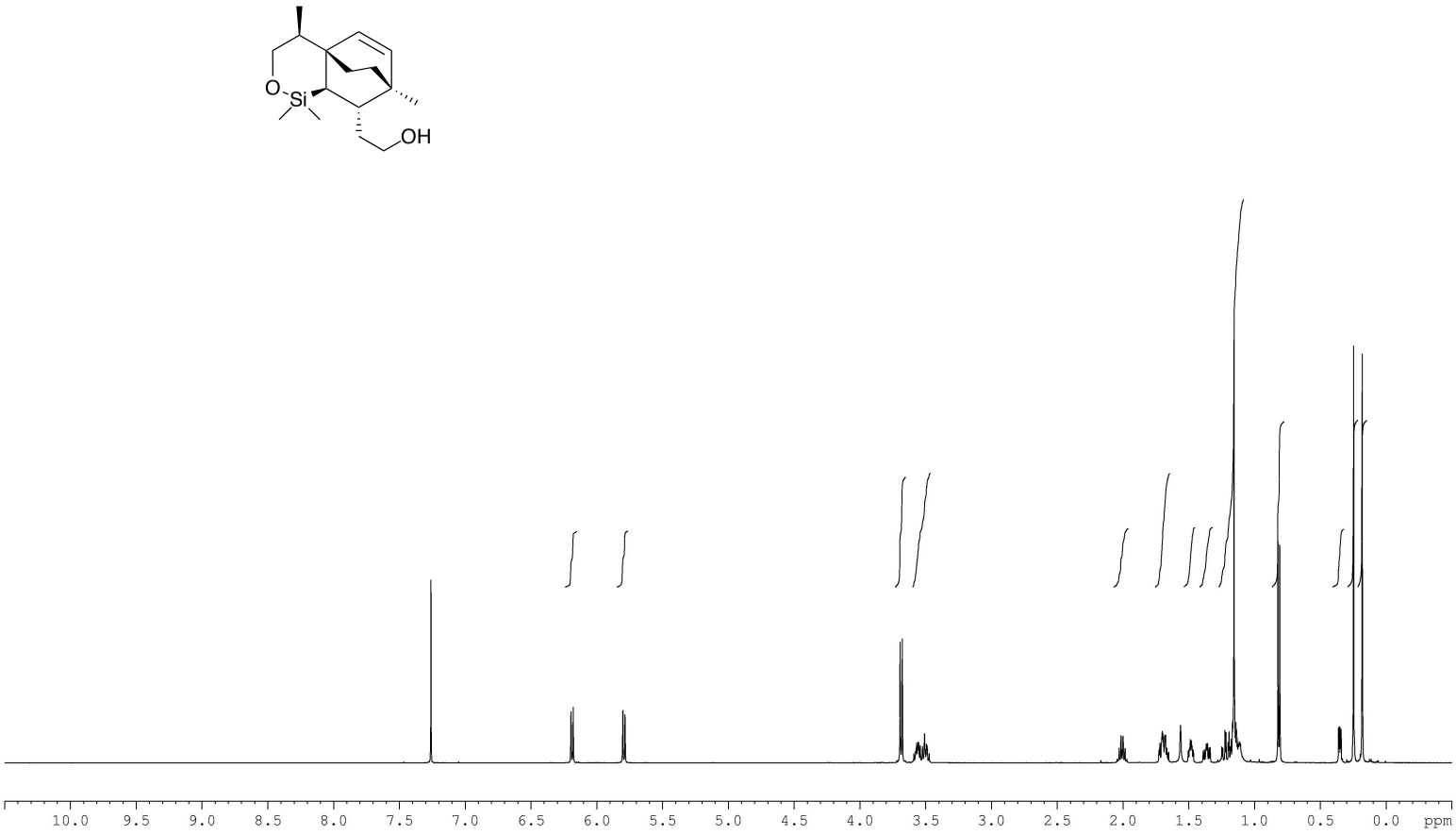



**Figure A2-1:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**3.1** in $CDCl_3$

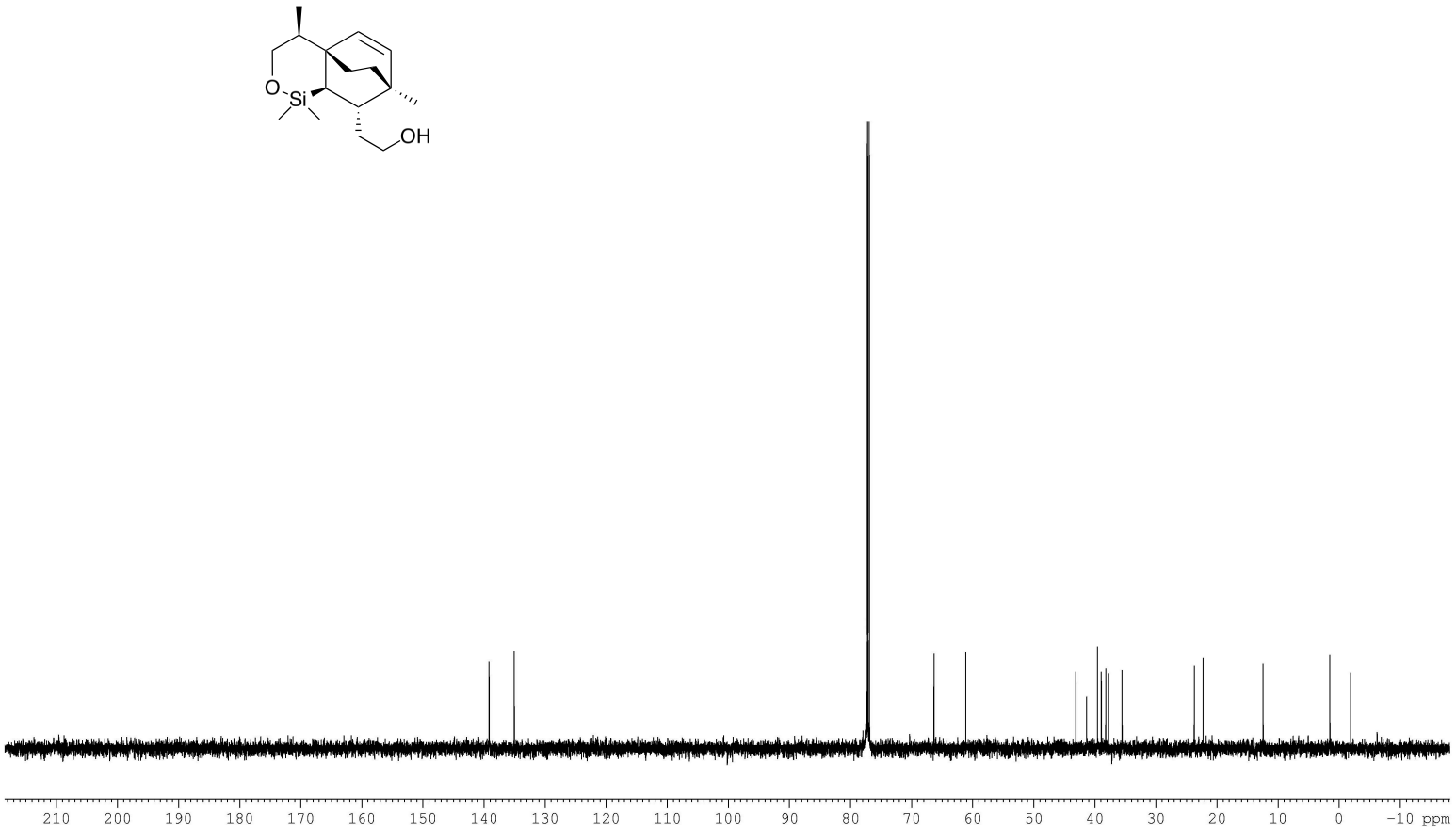



**Figure A2-2:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**3.1** in $CDCl_3$

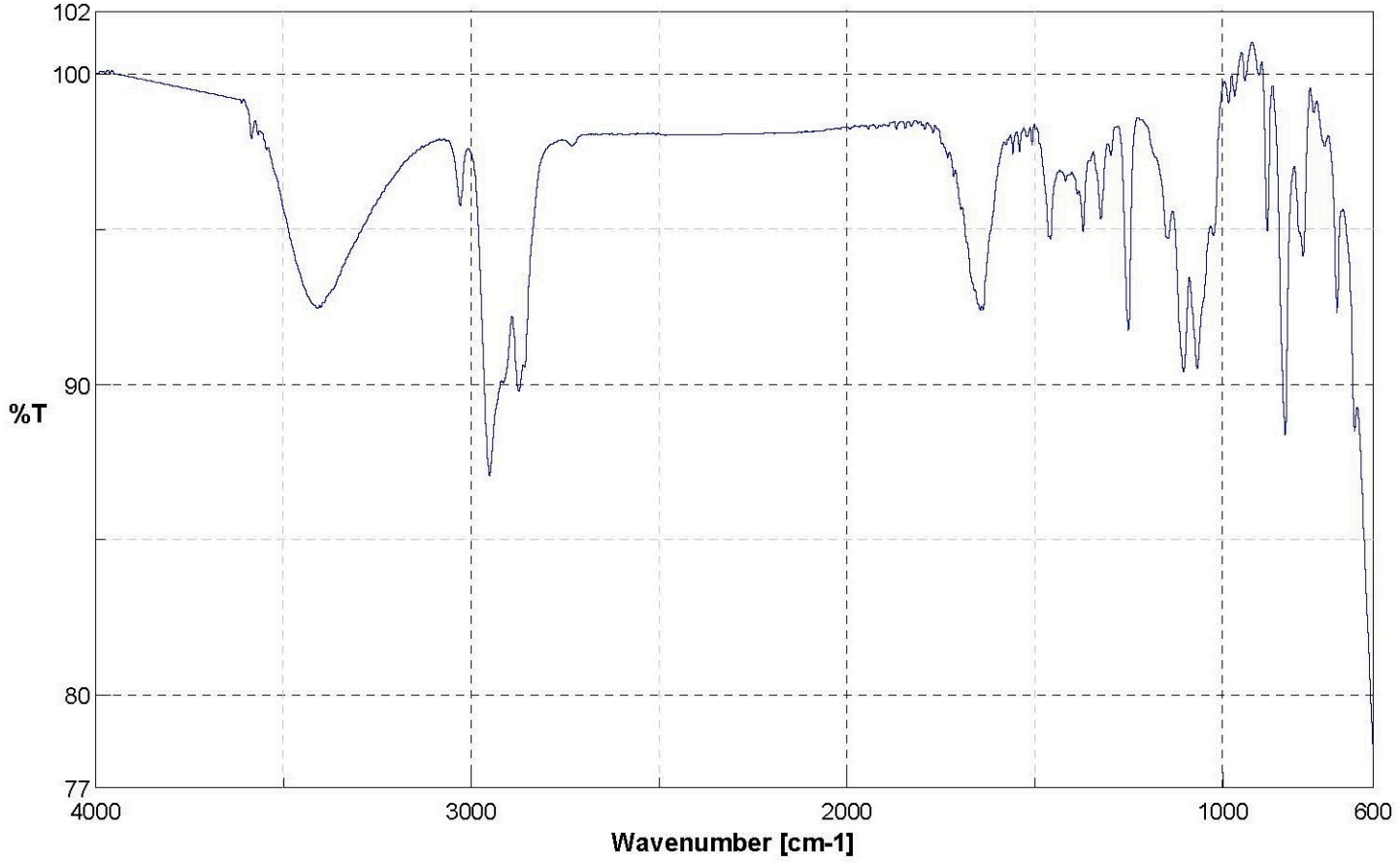



**Figure A2-3:** The Infrared Spectrum of Compound (–)-**3.1**

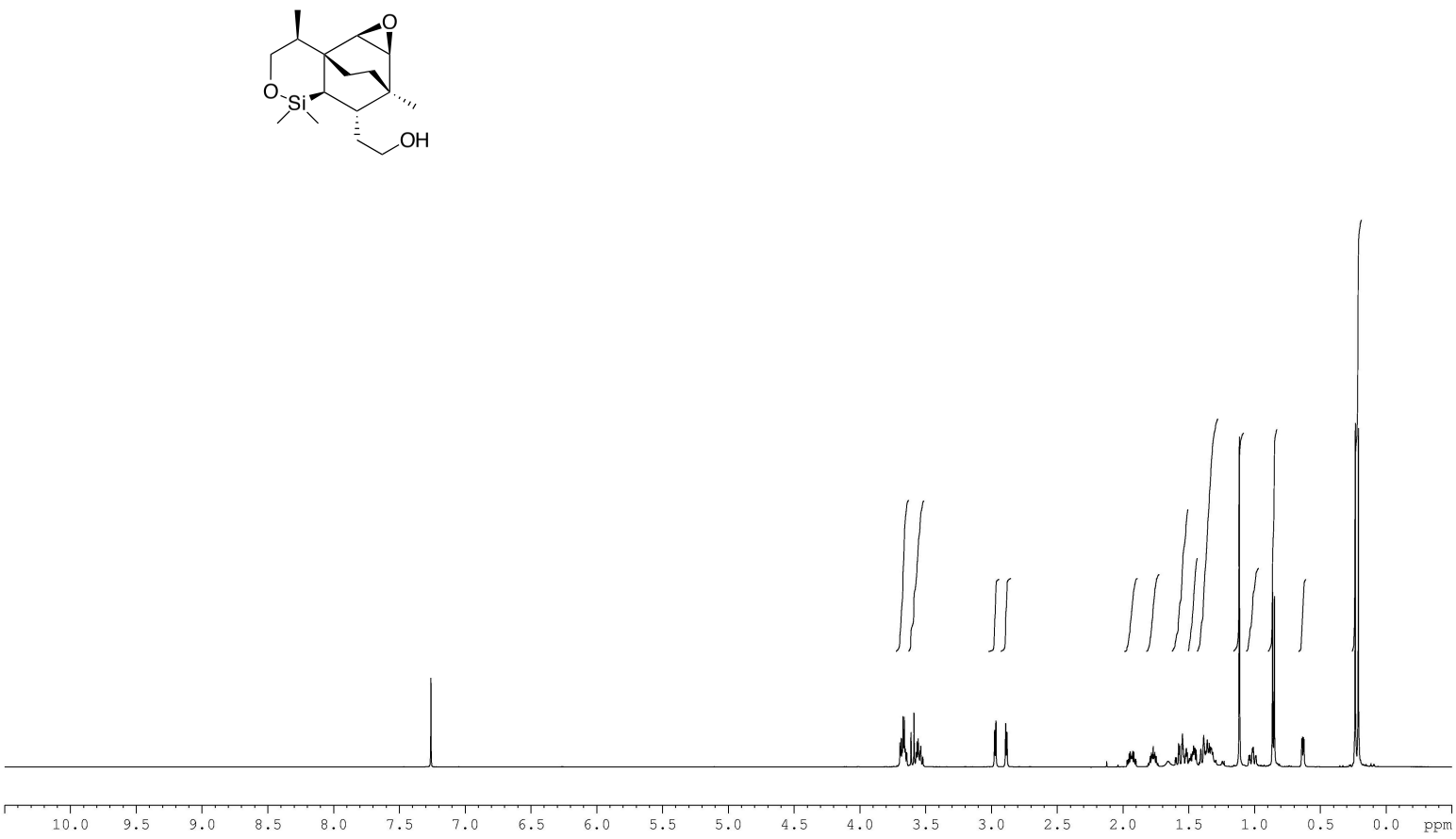



**Figure A2-4:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**3.2** in $CDCl_3$

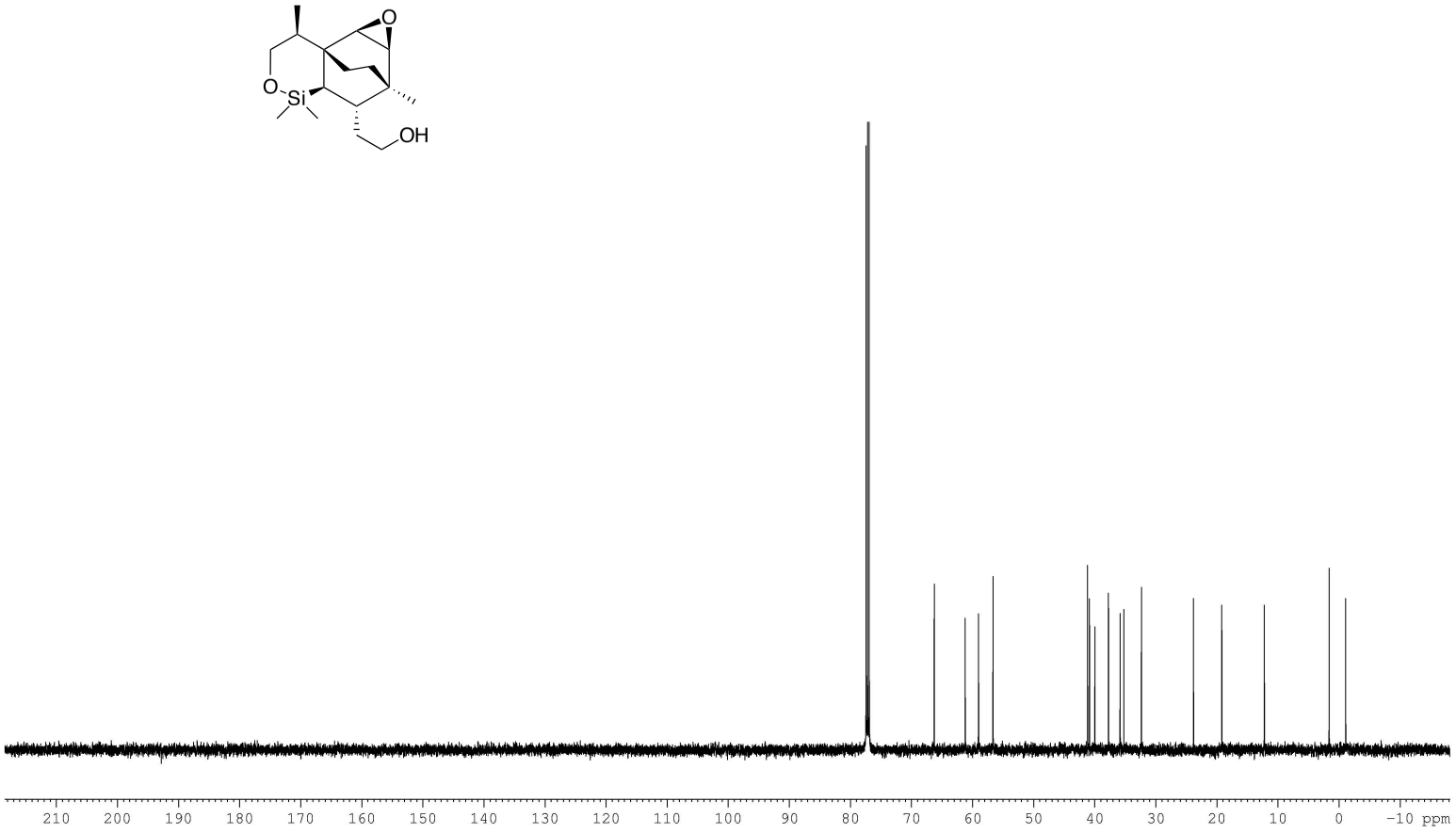



**Figure A2-5:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**3.2** in $CDCl_3$

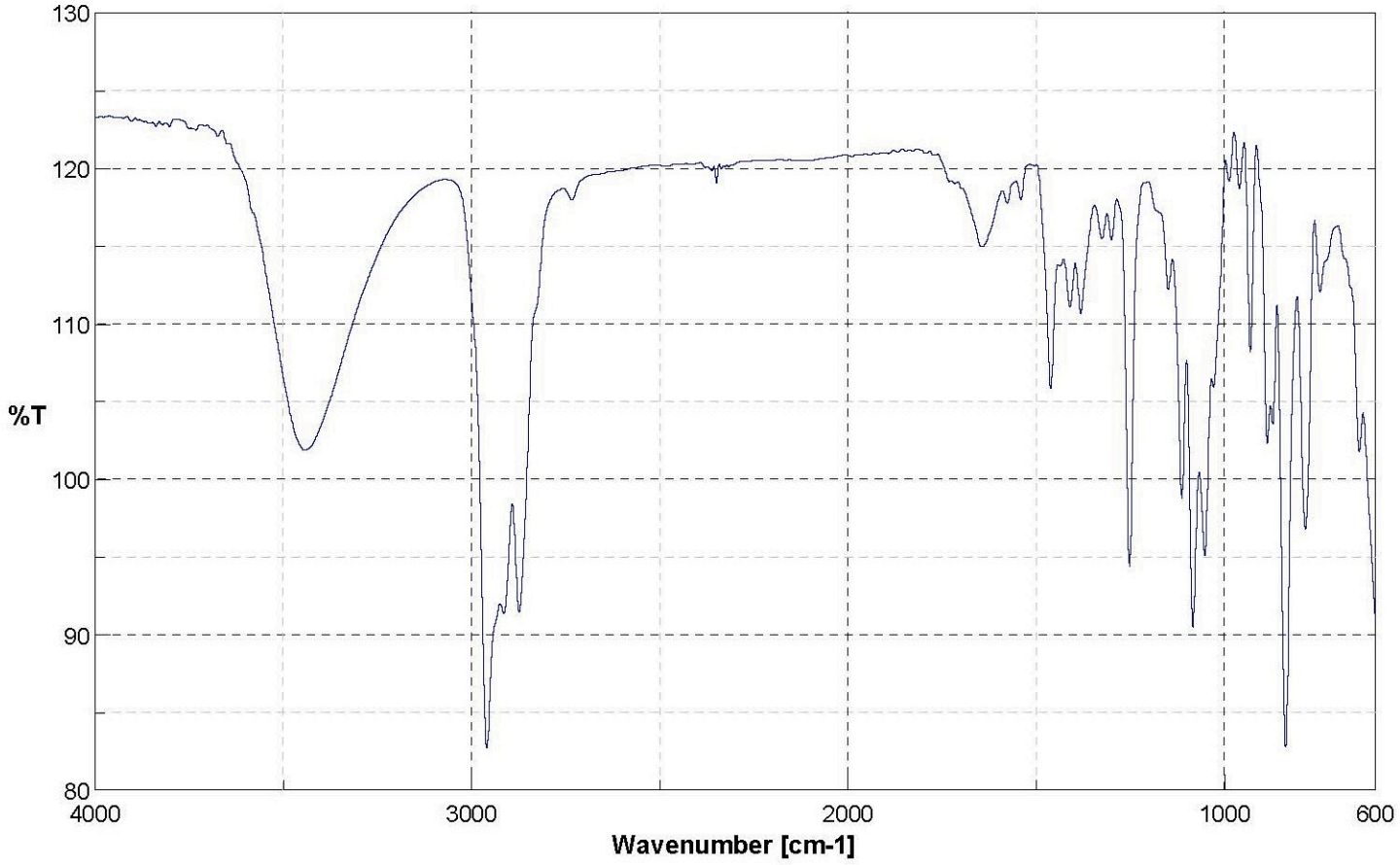



**Figure A2-6:** The Infrared Spectrum of Compound (–)-**3.2**

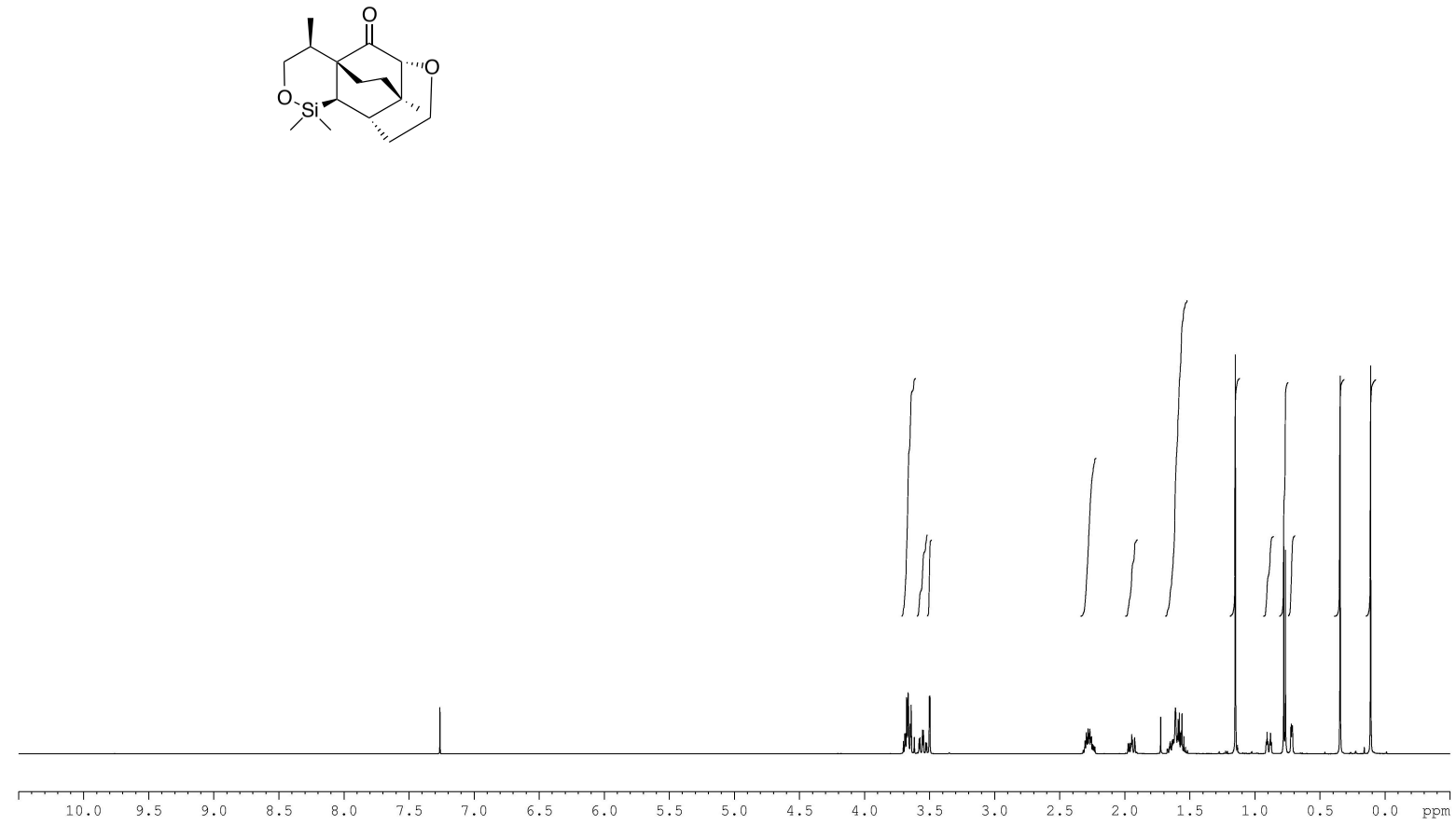



**Figure A2-7:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.3** in $CDCl_3$

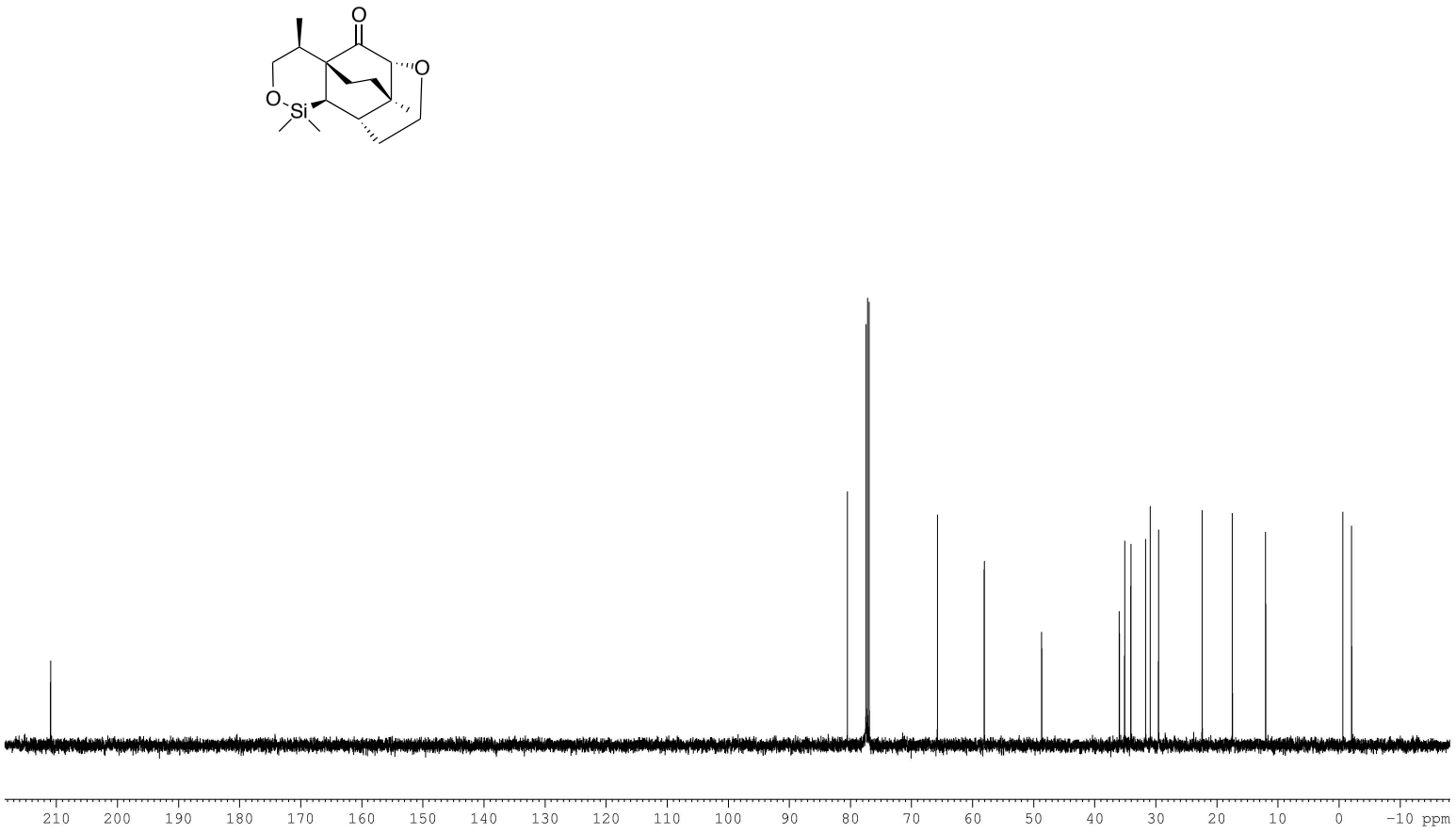



**Figure A2-8:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.3** in $CDCl_3$

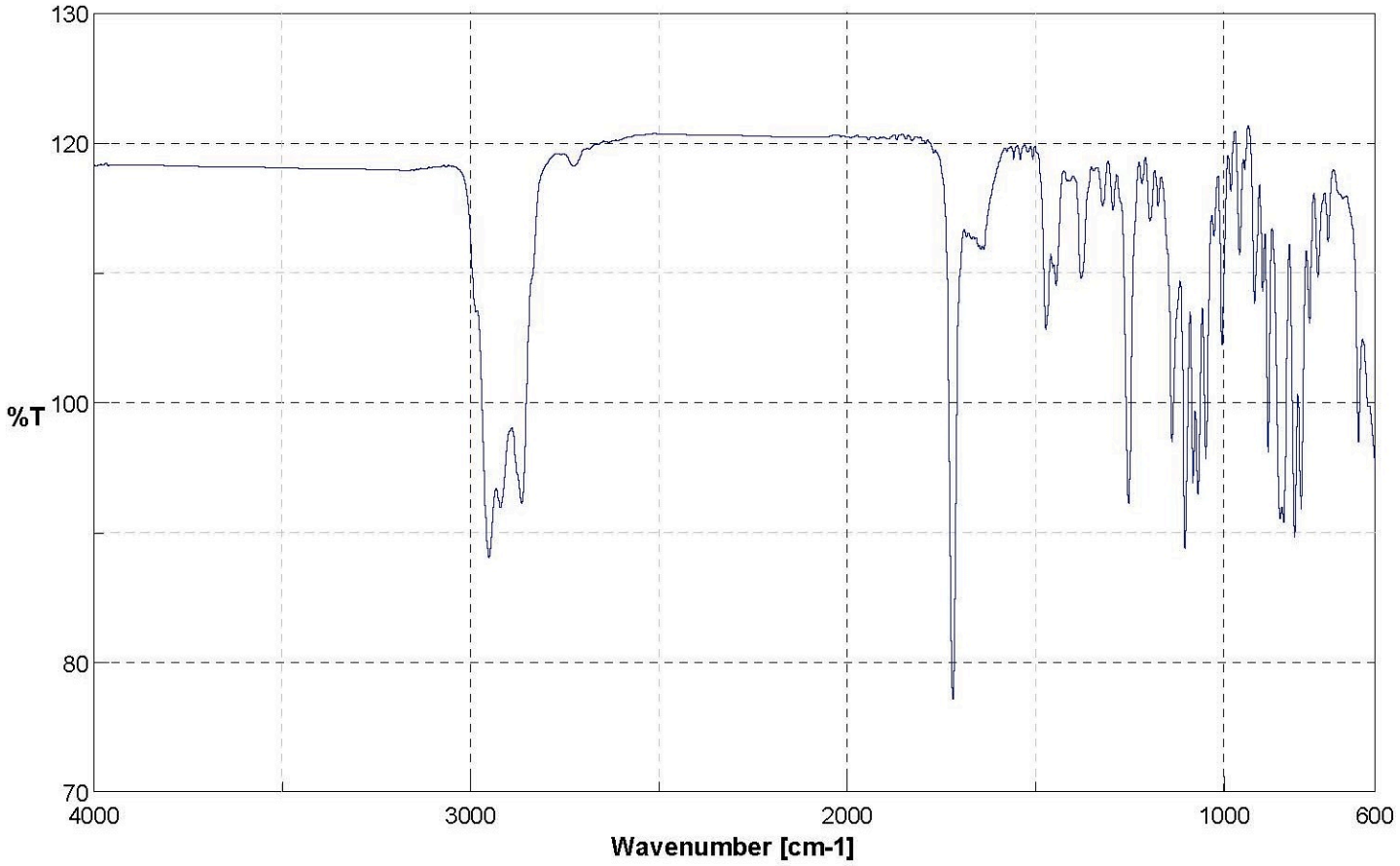



**Figure A2-9:** The Infrared Spectrum of Compound (+)-**3.3**

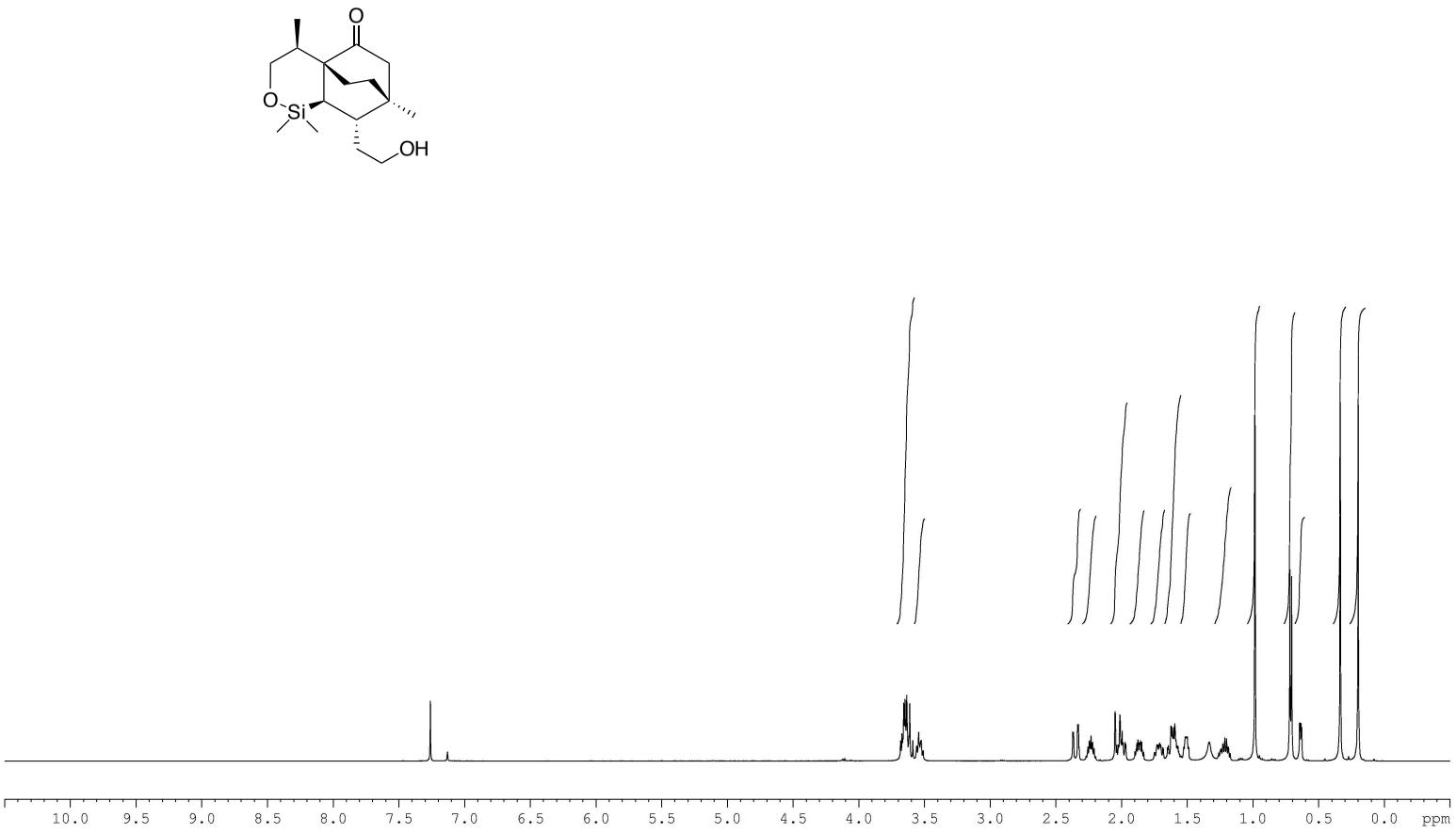



**Figure A2-10:** The 500 MHz $^{1}H$ NMR Spectrum of Comopund (+)-**3.7** in $CDCl_3$

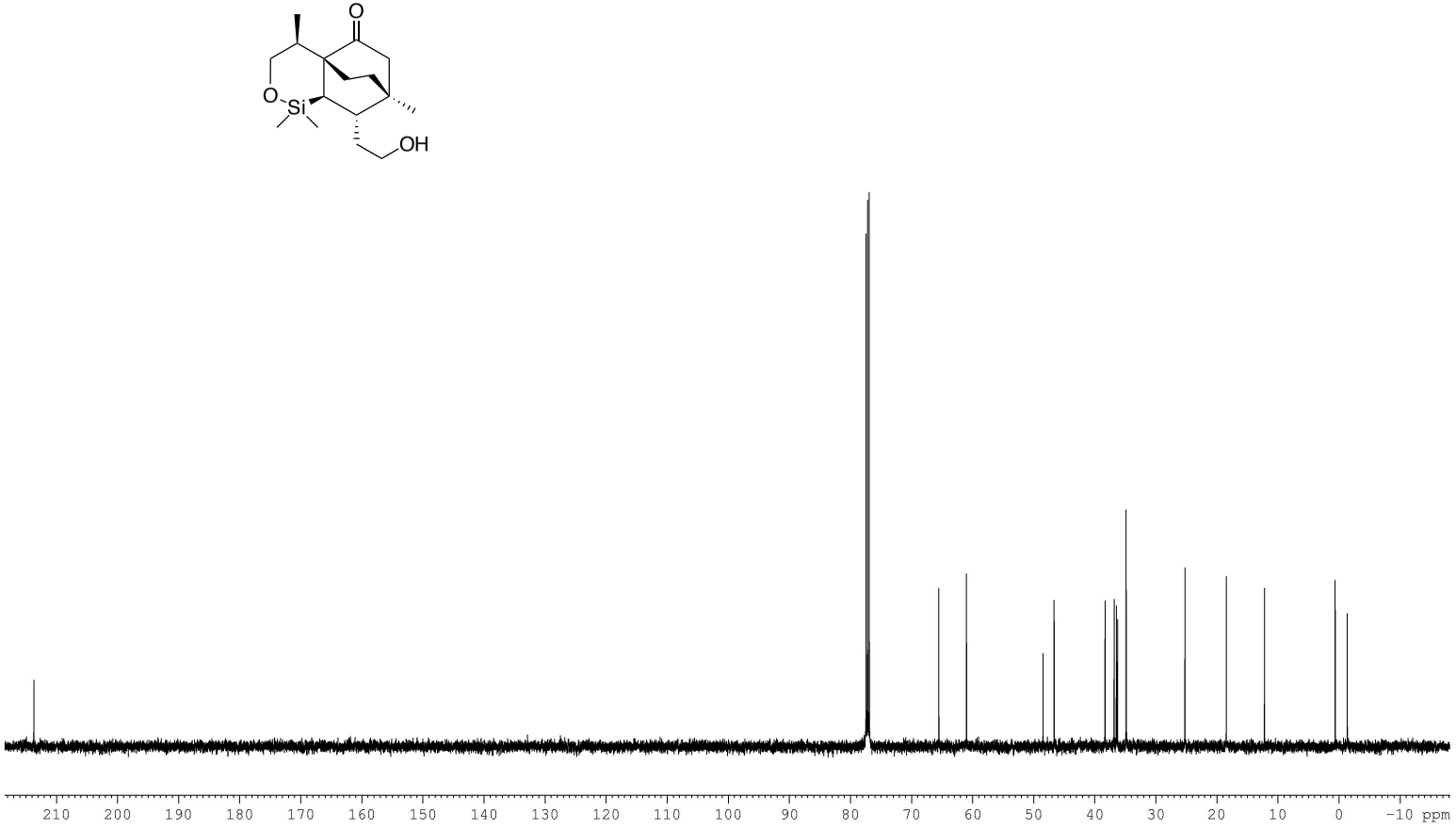



**Figure A2-11:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.7** in $CDCl_3$

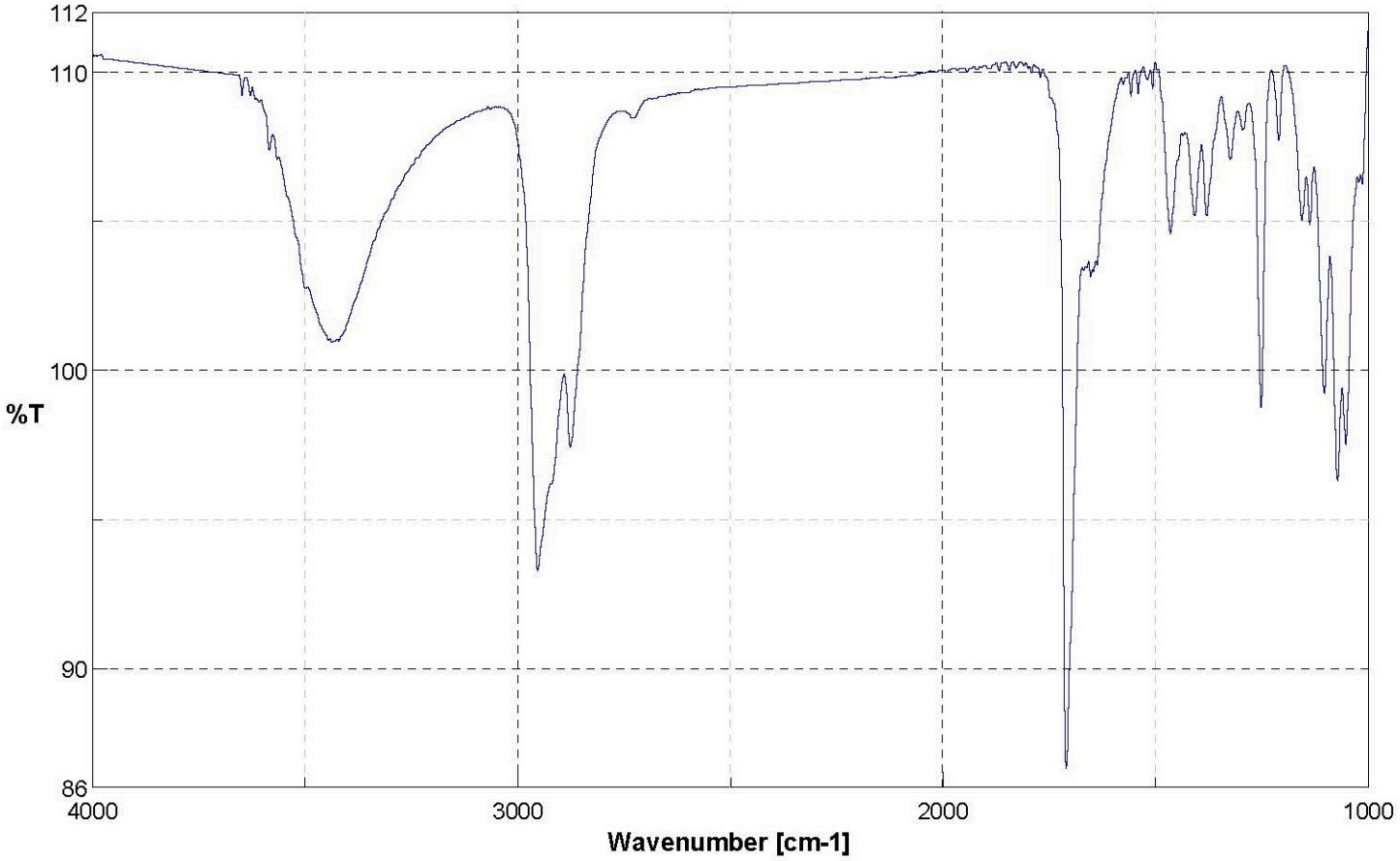



**Figure A2-12:** The Infrared Spectrum of Compound (+)-**3.7**

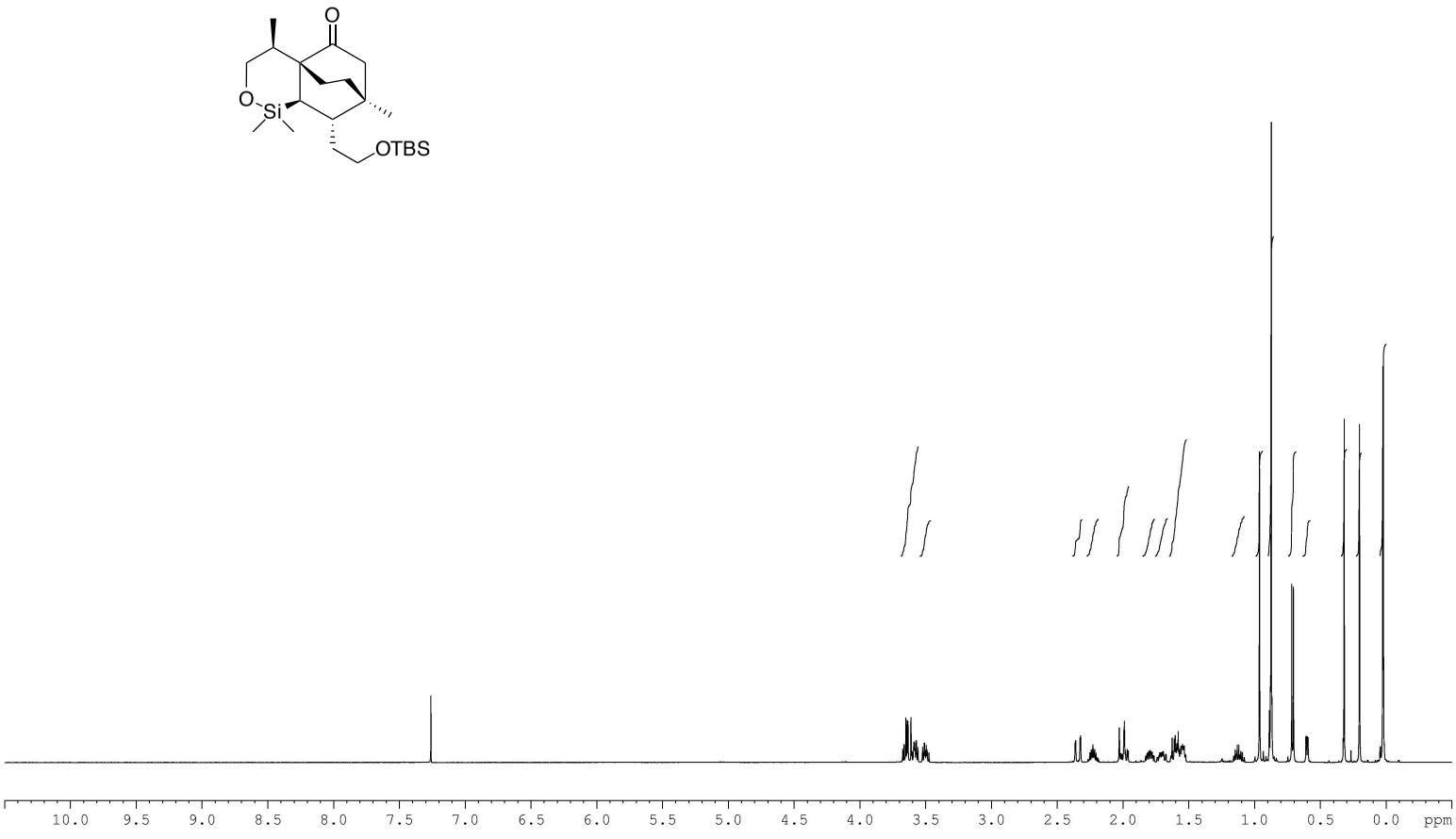



**Figure A2-13:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.6** in $CDCl_3$

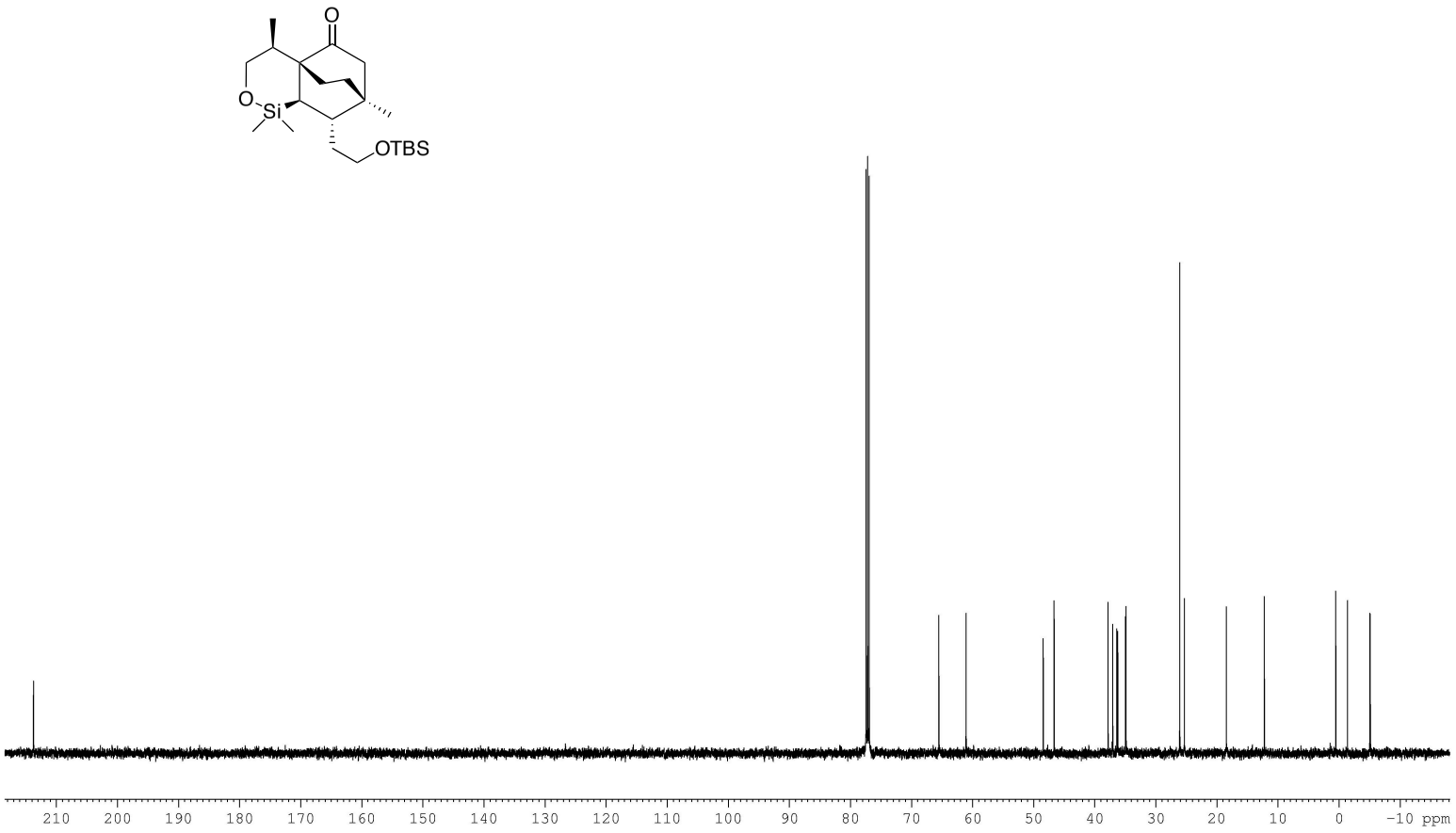



**Figure A2-14:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.6** in $CDCl_3$

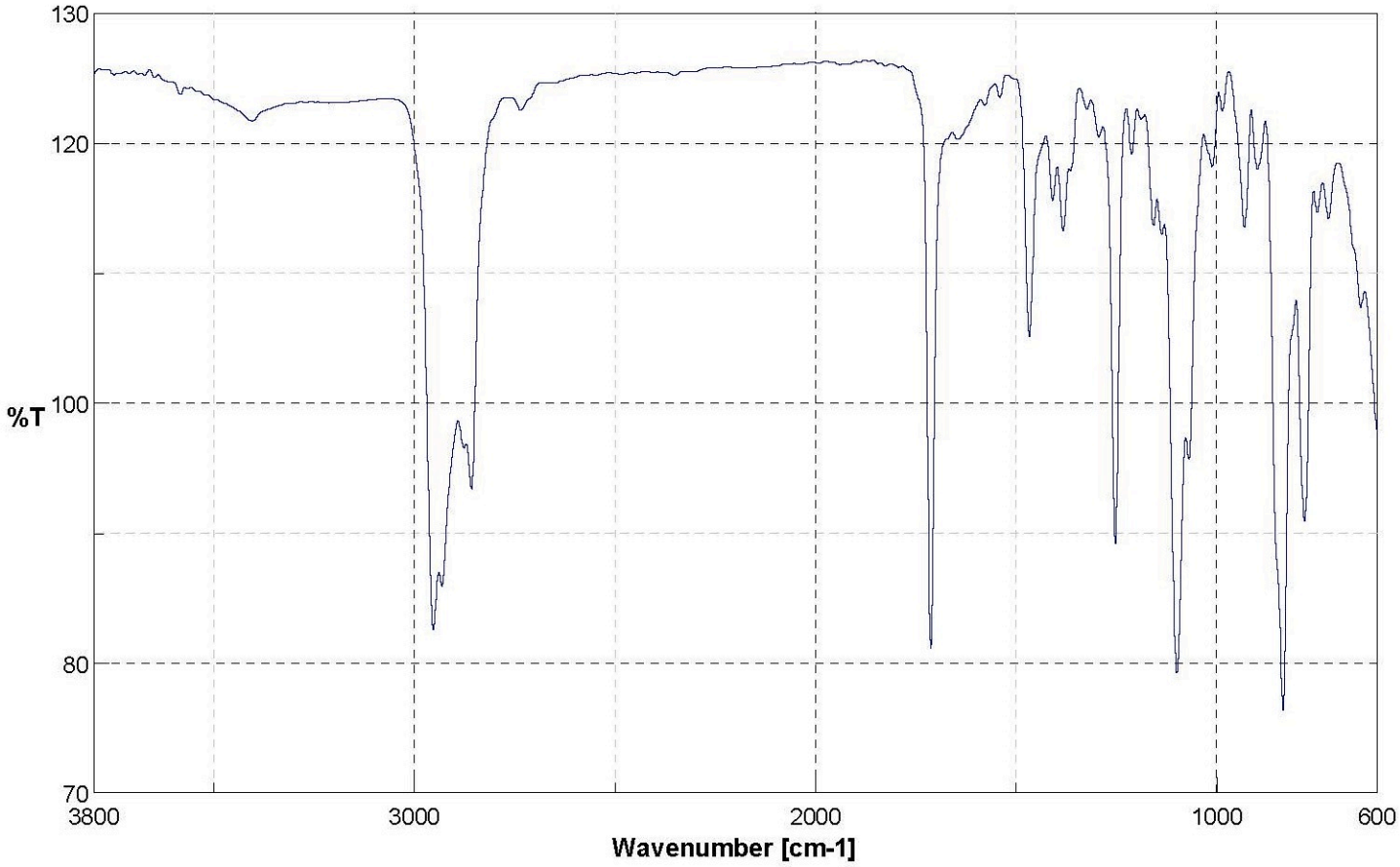



**Figure A2-15:** The Infrared Spectrum of Compound (+)-**3.6**

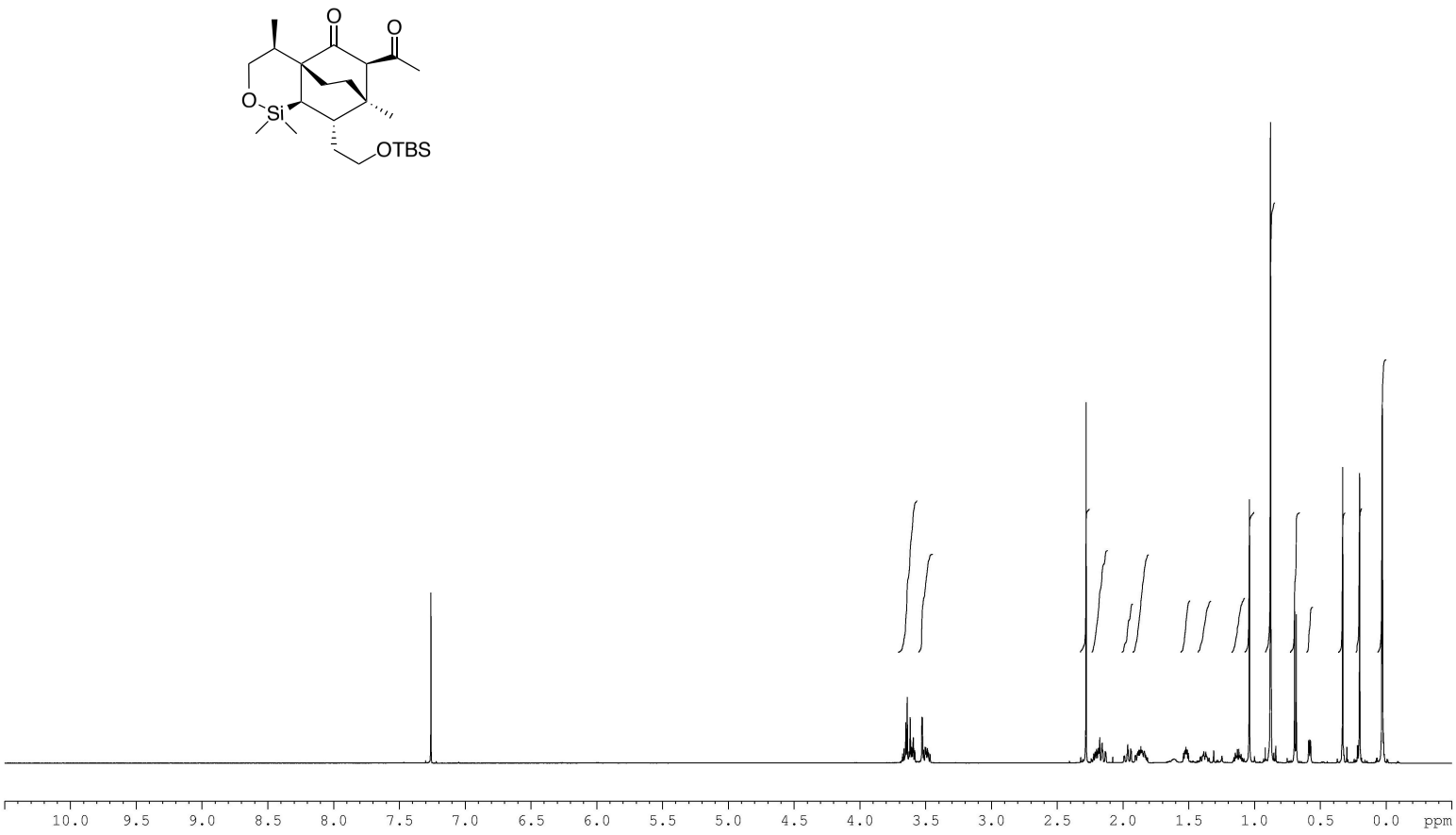



**Figure A2-16:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.8** in $CDCl_3$

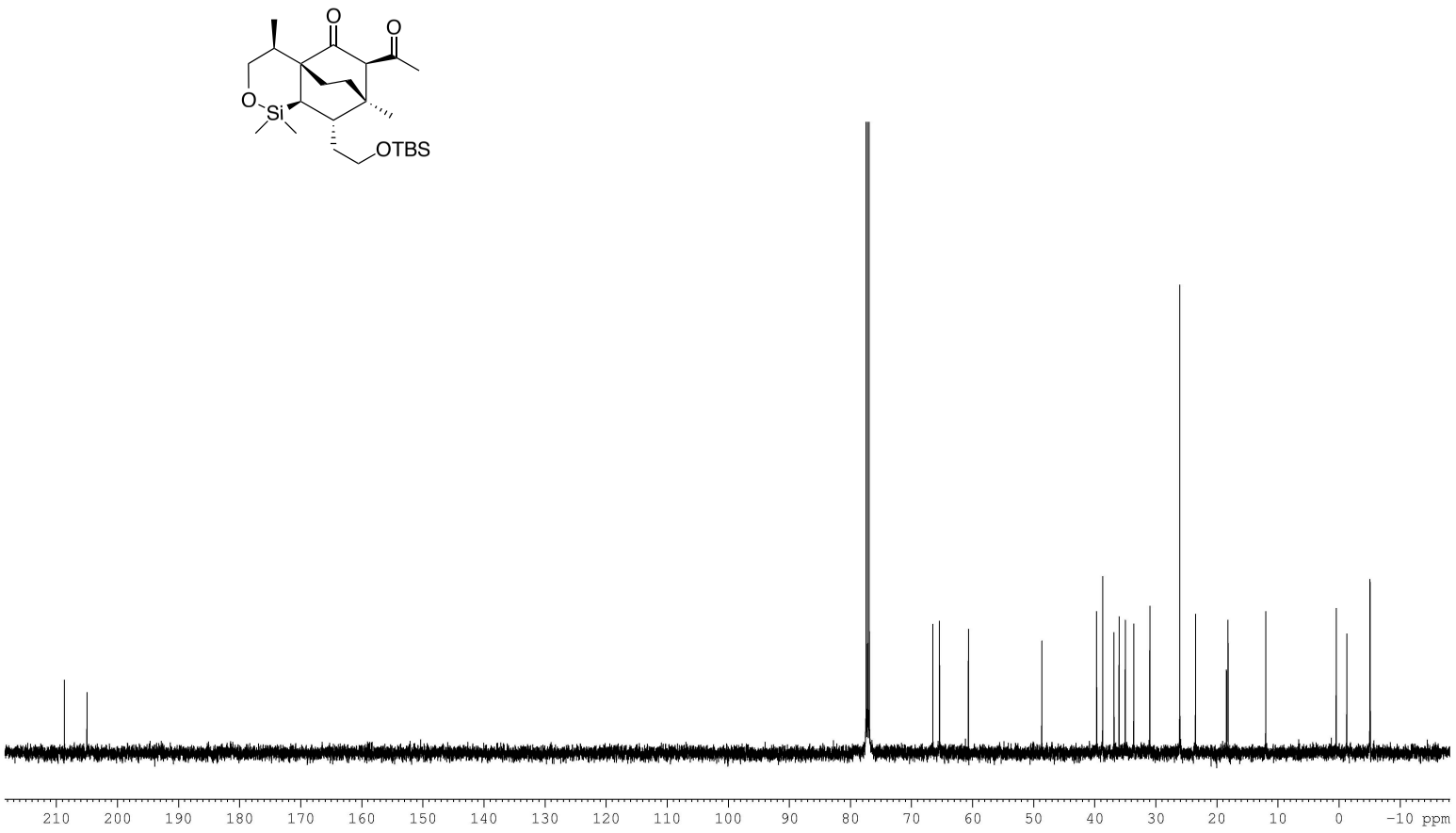



**Figure A2-17:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.8** in $CDCl_3$

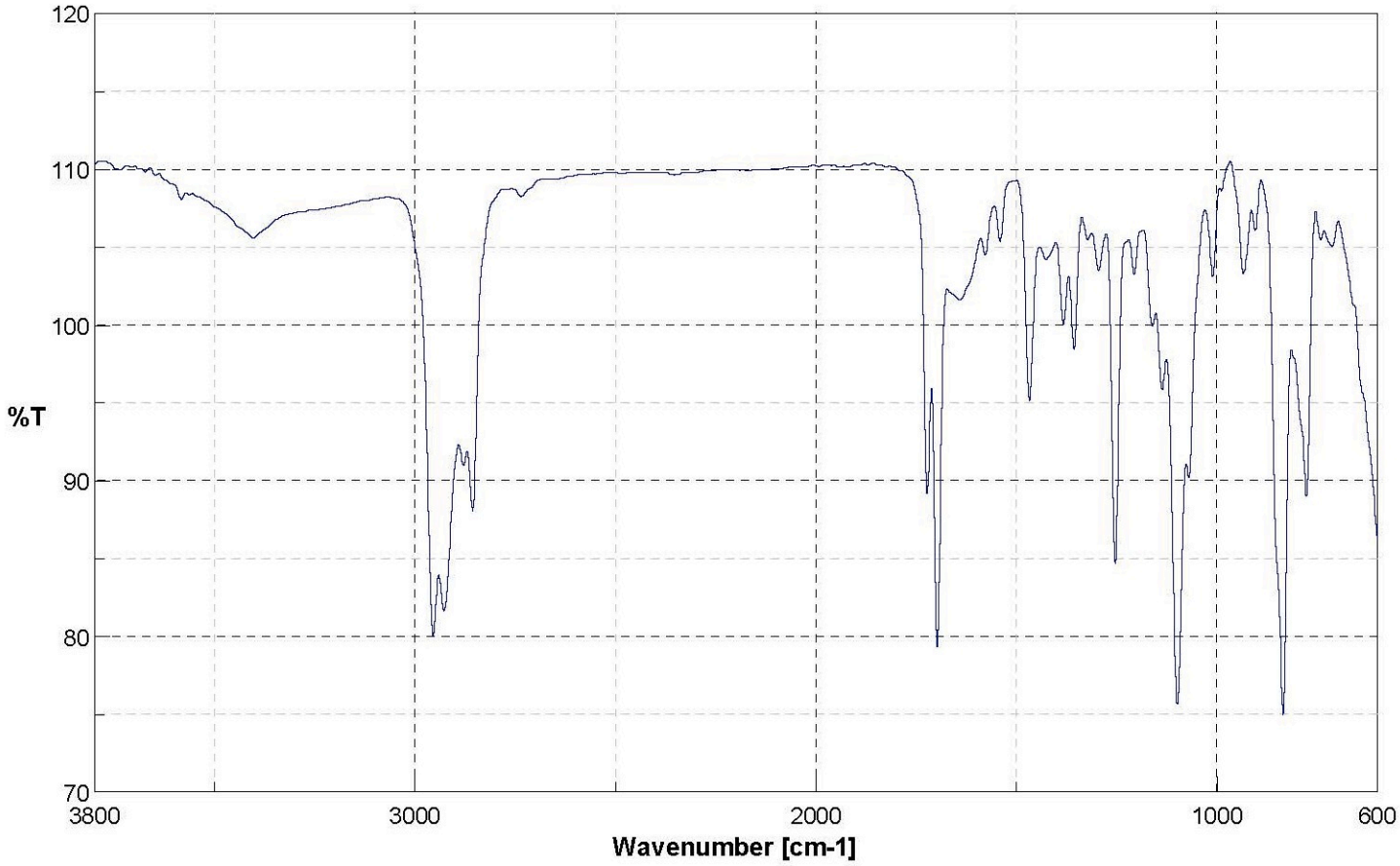



**Figure A2-18:** The Infrared Spectrum of Compound (+)-**3.8**

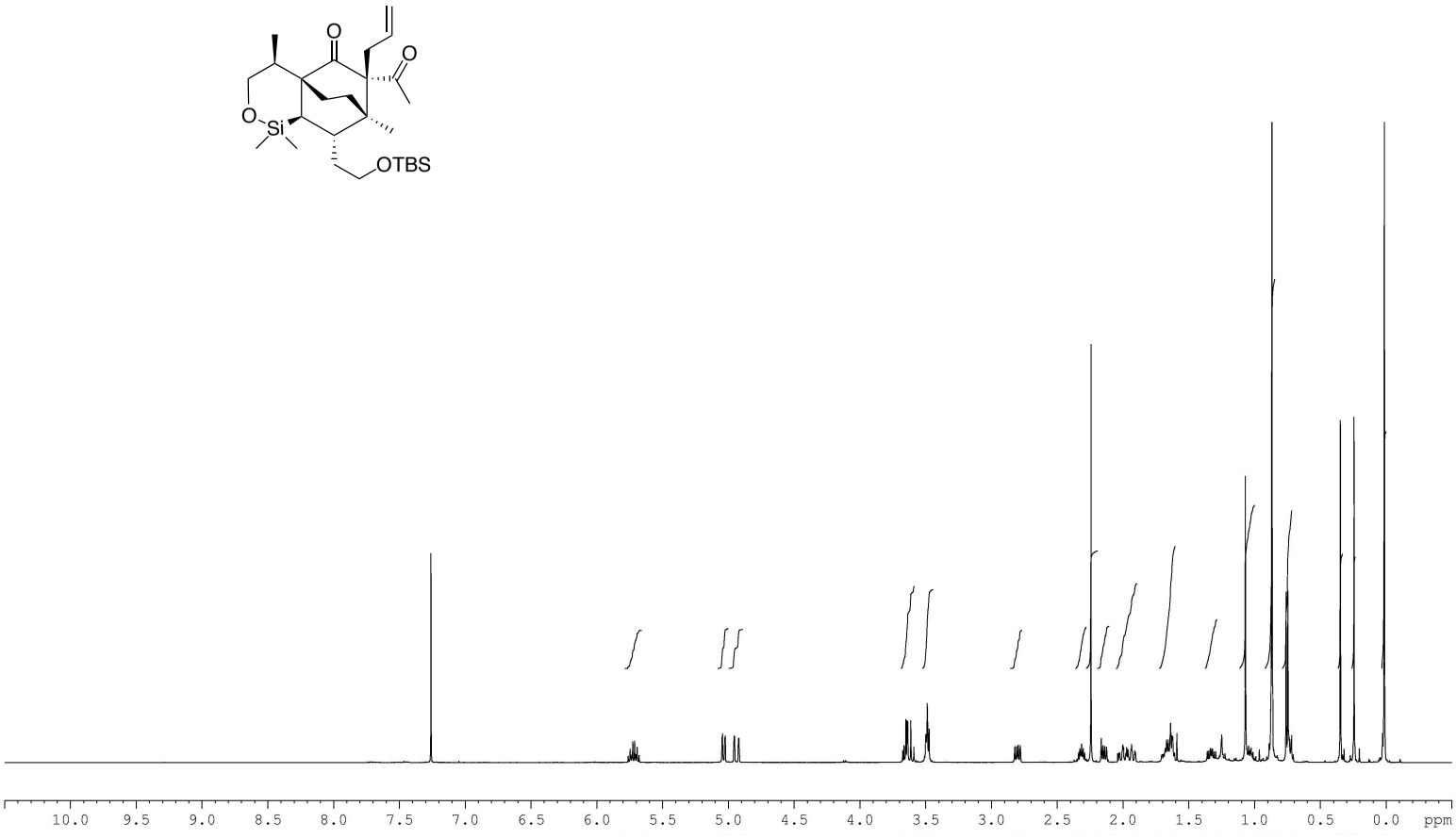



**Figure A2-19:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**3.10** in $CDCl_3$

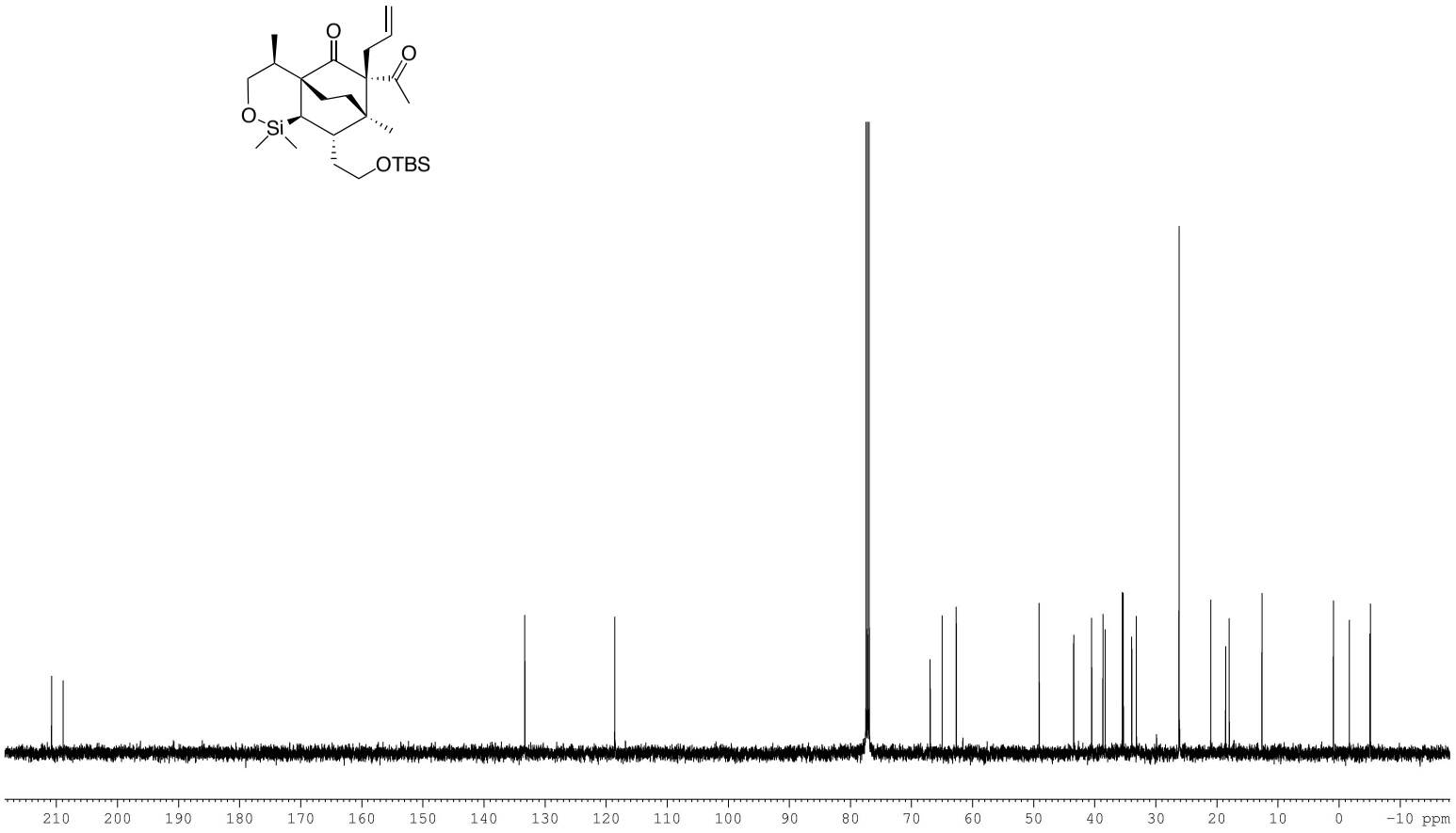



**Figure A2-20:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**3.10** in $CDCl_3$

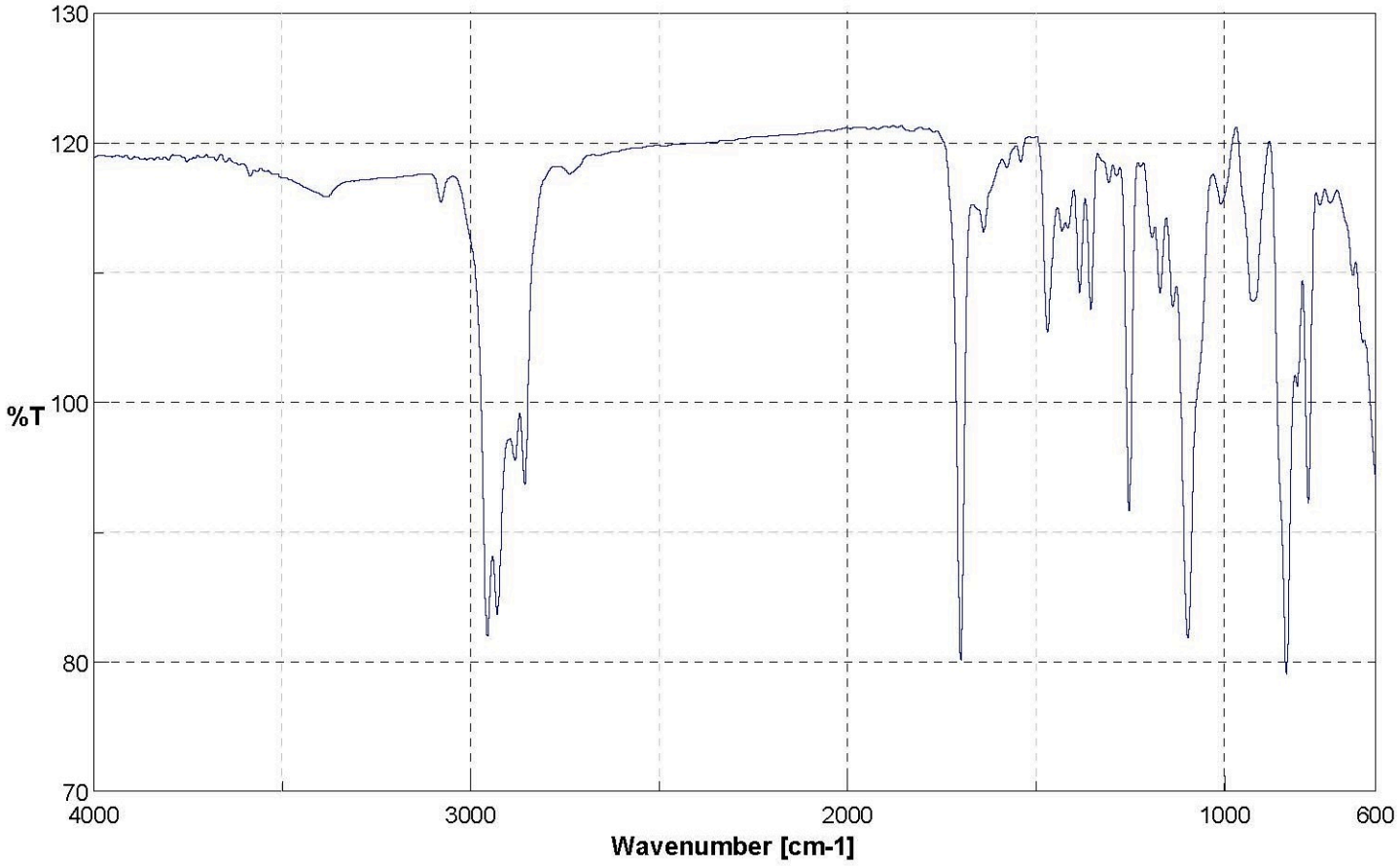



**Figure A2-21:** The Infrared Spectrum of Compound (–)-**3.10**

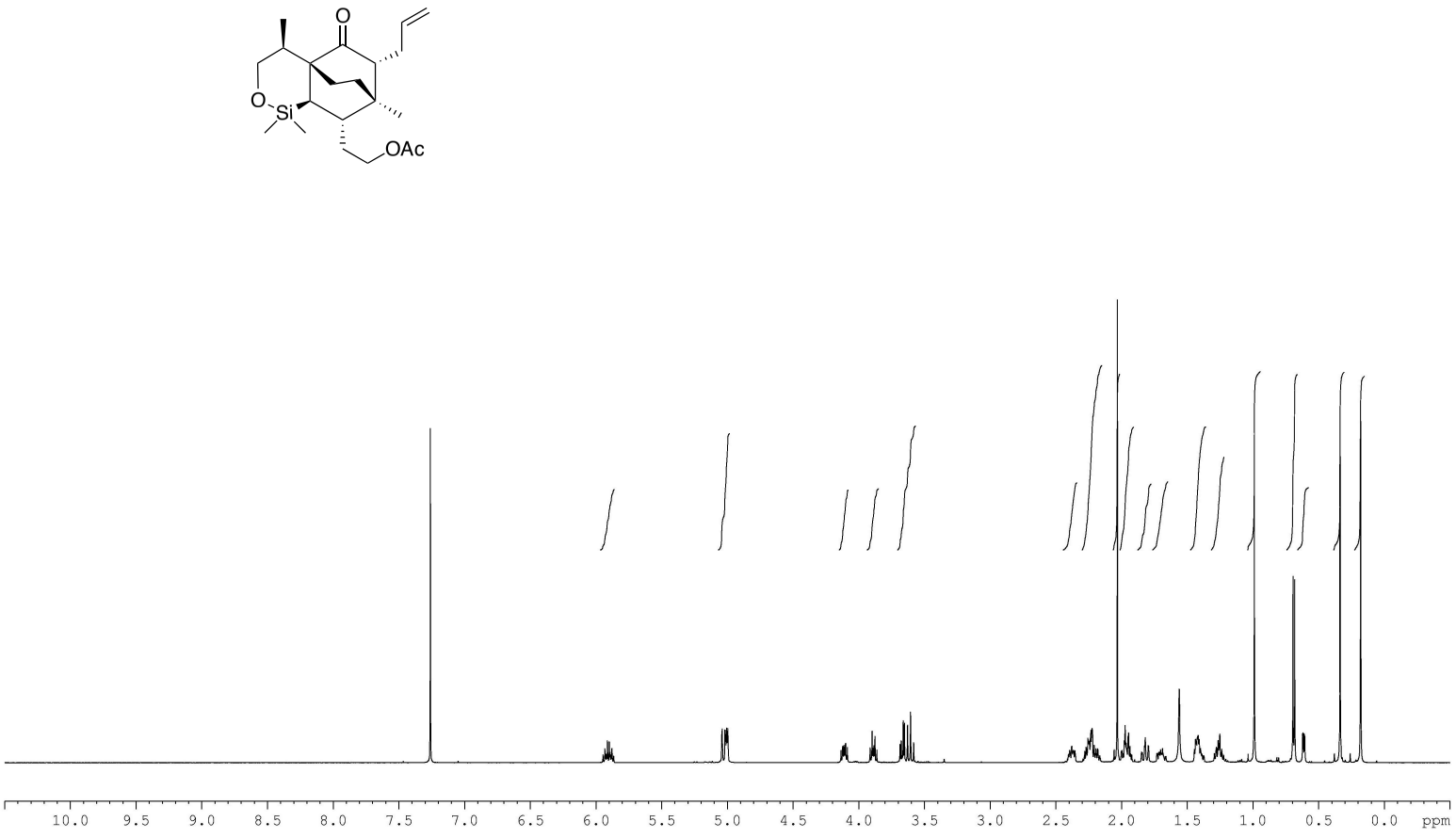



**Figure A2-22:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.12** in $CDCl_3$

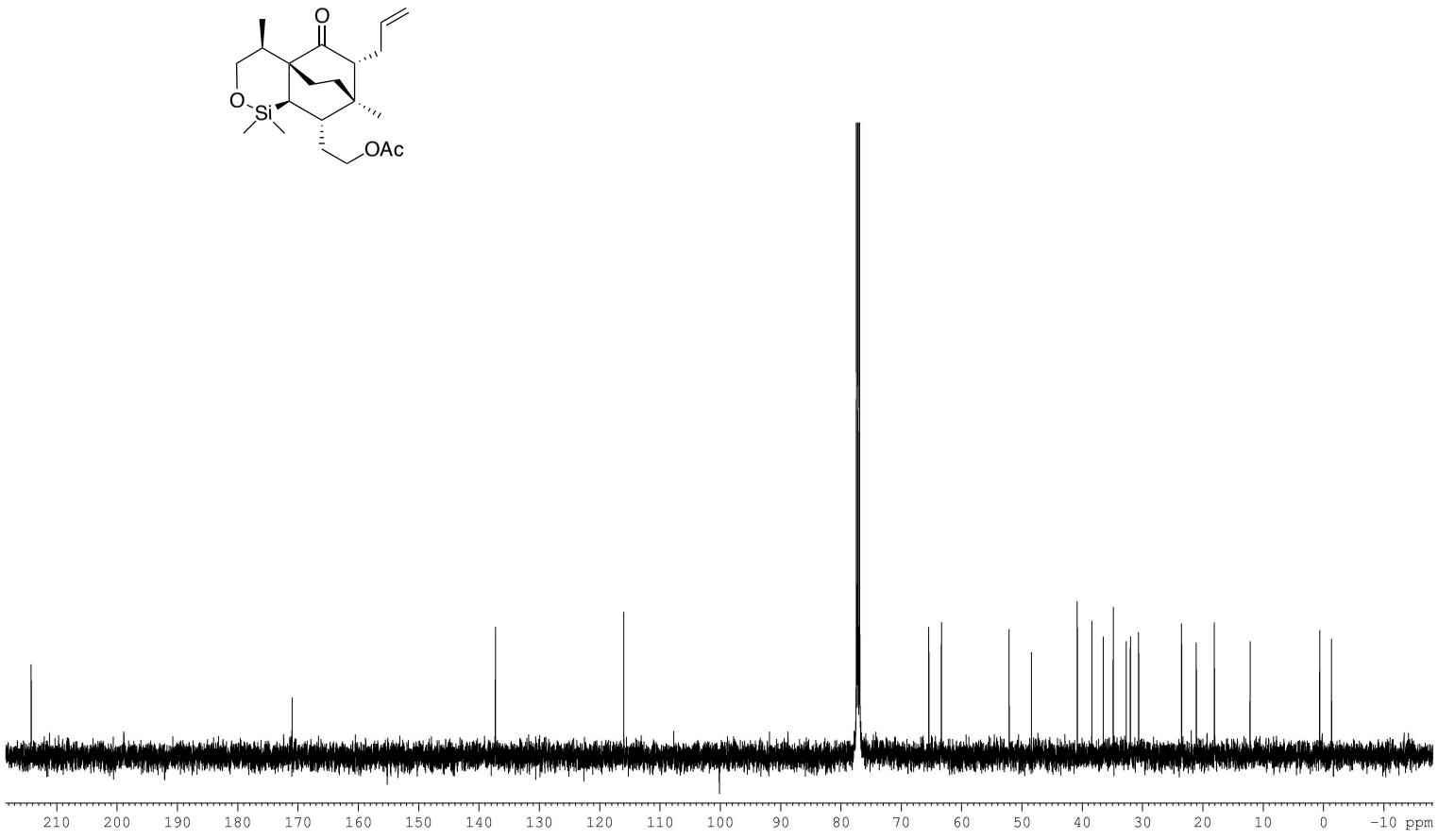



**Figure A2-23:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.12** in $CDCl_3$

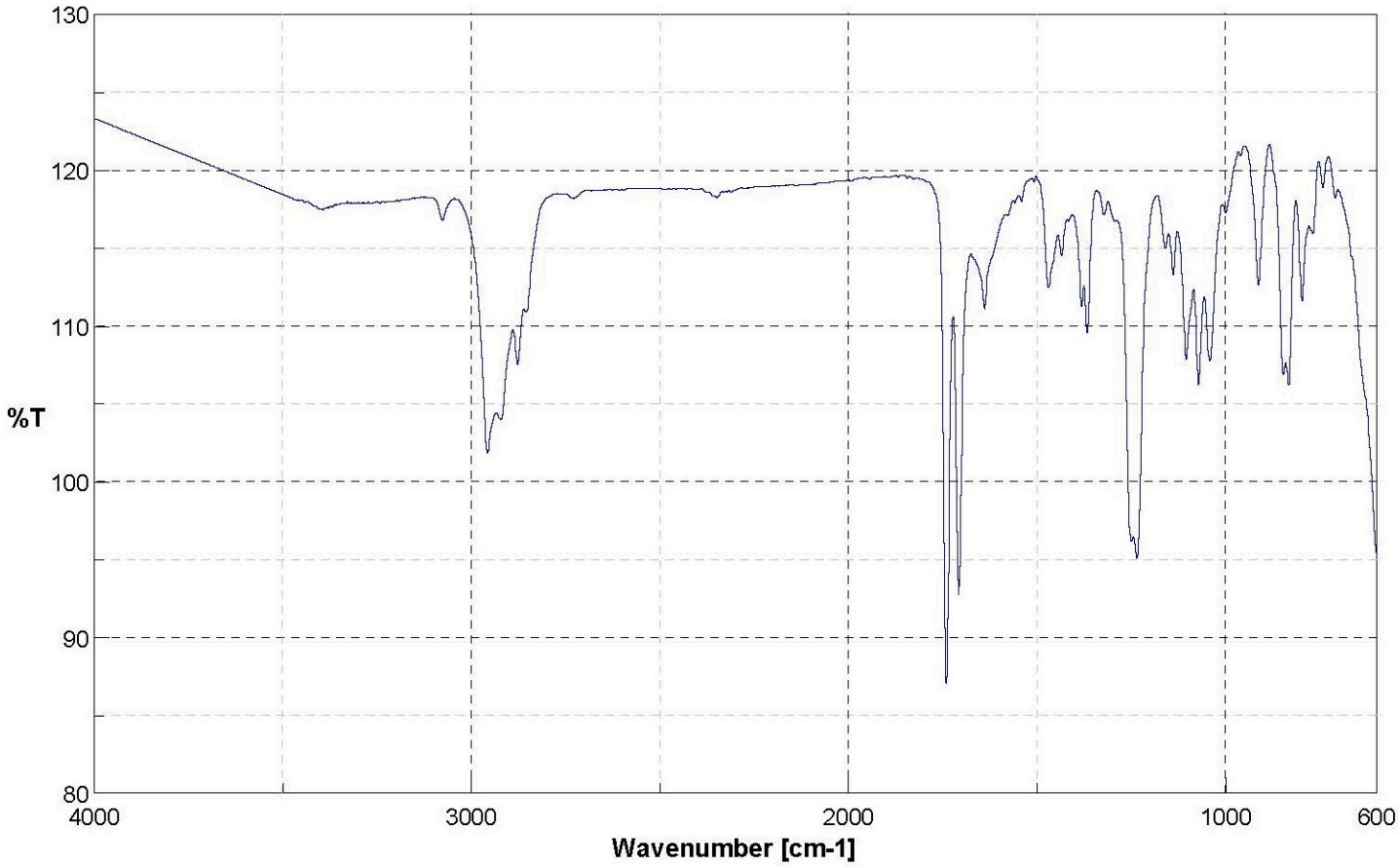



**Figure A2-24:** The Infrared Spectrum of Compound (+)-**3.12**

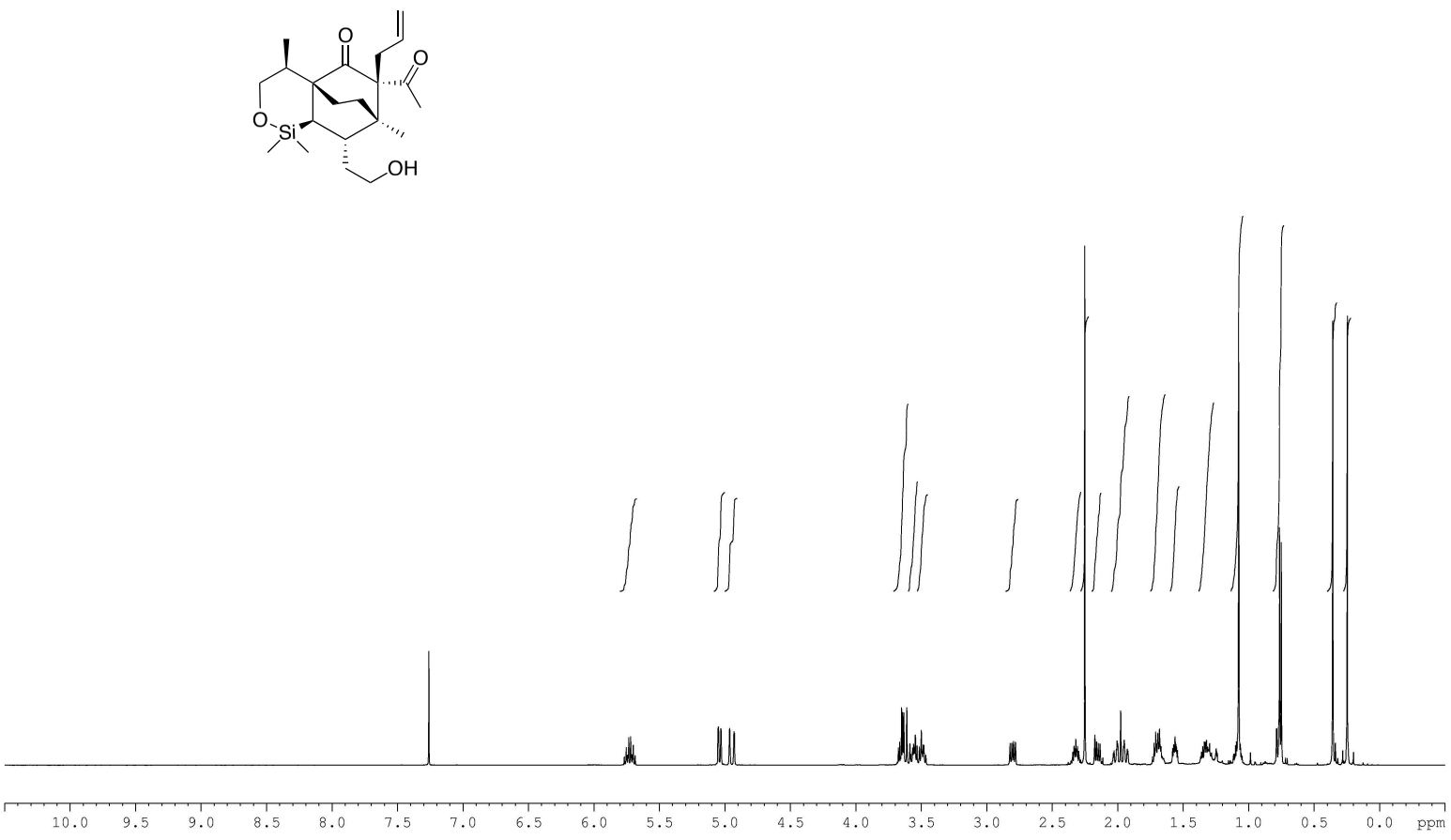



**Figure A2-25:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**3.11** in $CDCl_3$

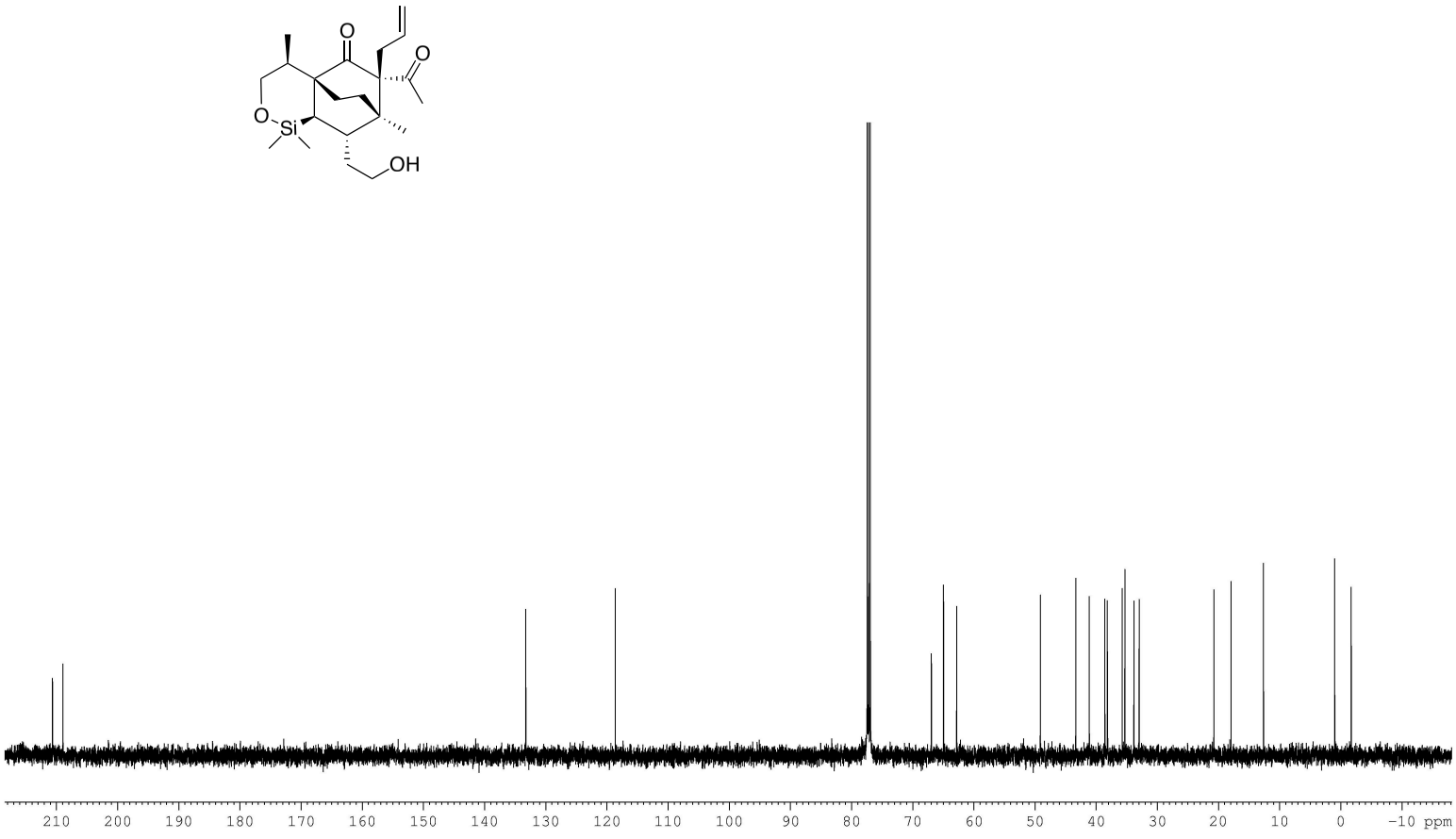



**Figure A2-26:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**3.11** in $CDCl_3$

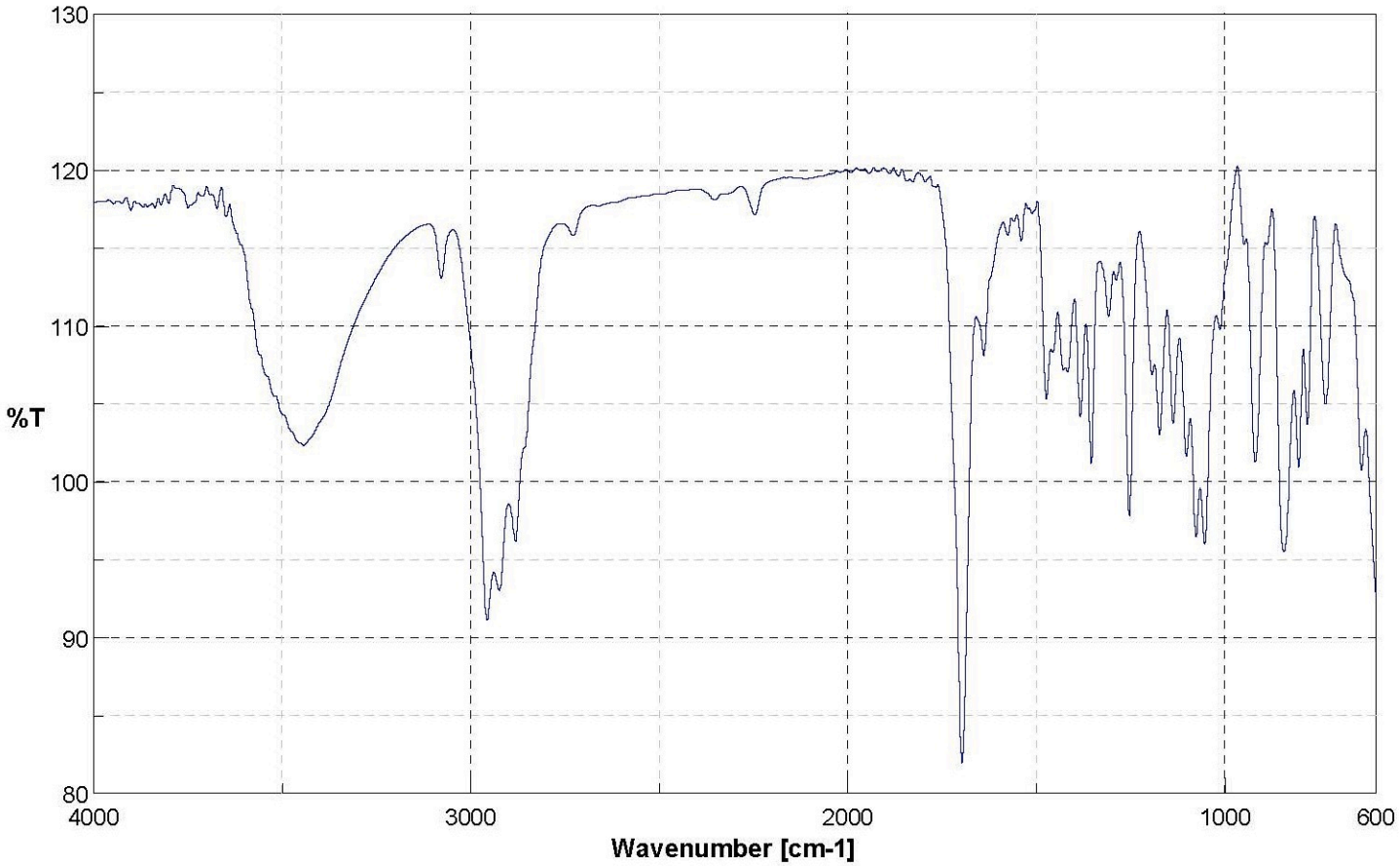



**Figure A2-27:** The Infrared Spectrum of Compound (–)-**3.11**

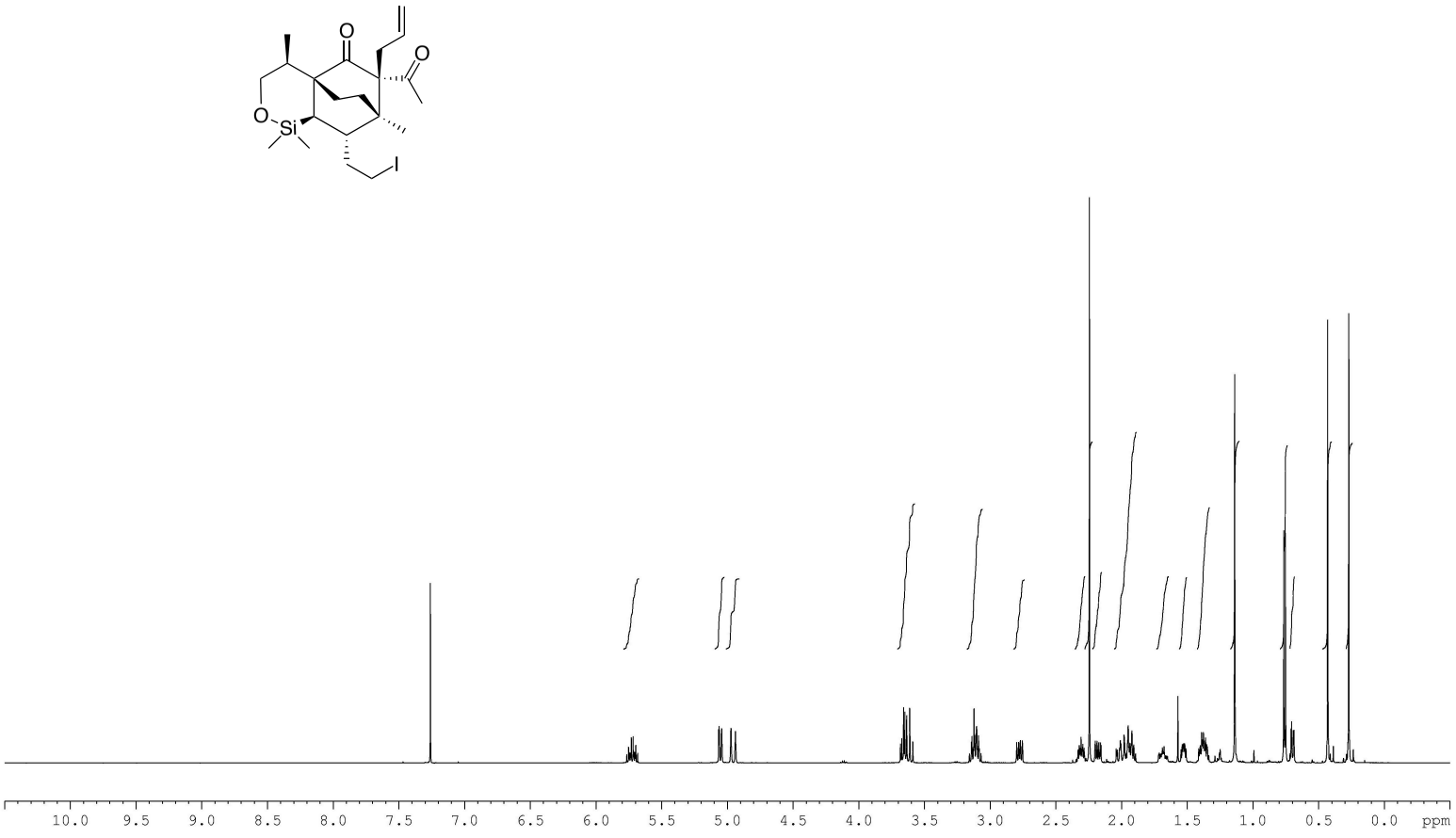



**Figure A2-28:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**3.5** in $CDCl_3$

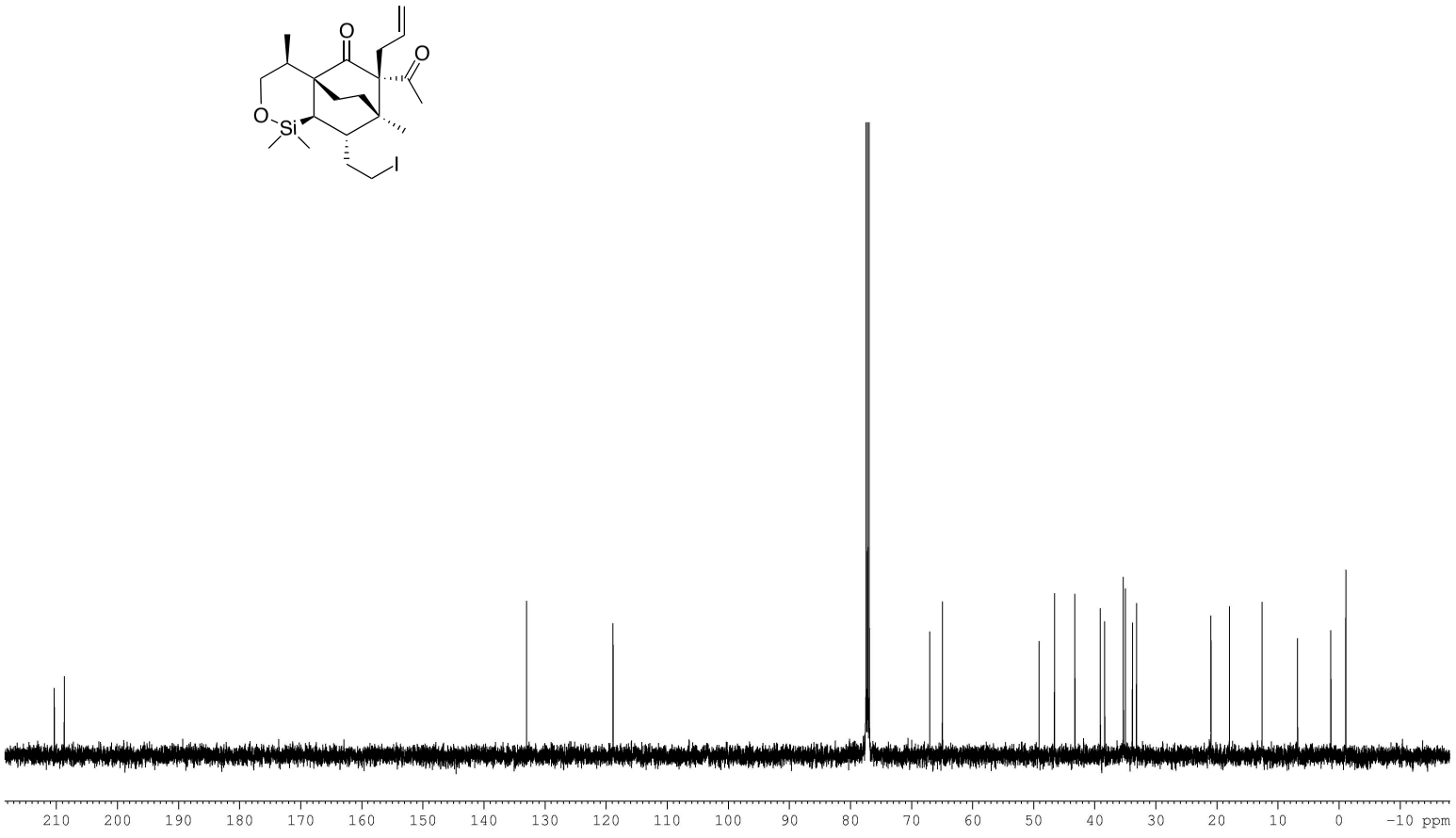



**Figure A2-29:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**3.5** in $CDCl_3$

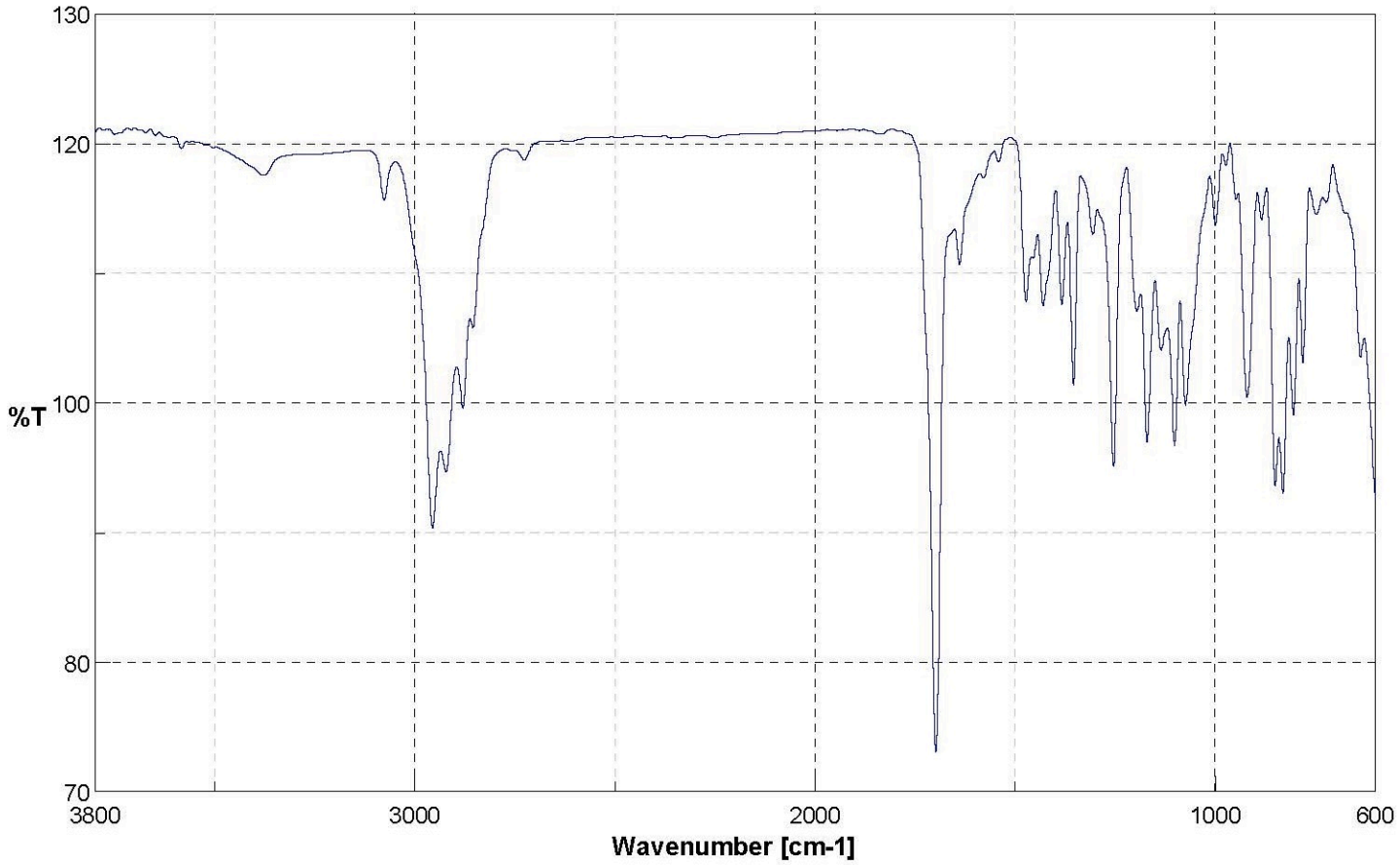



**Figure A2-30:** The Infrared Spectrum of Compound (–)-**3.5**

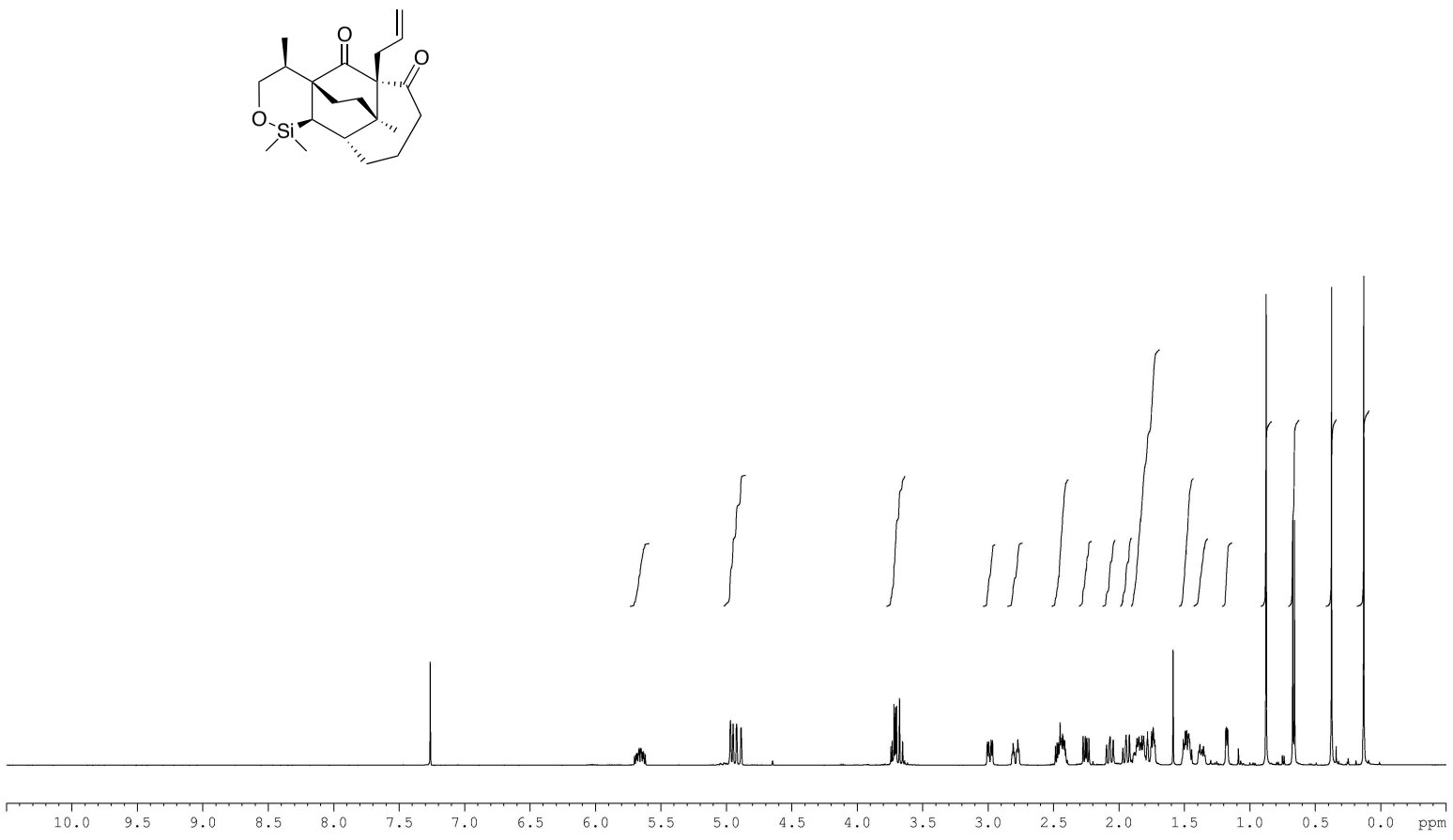



**Figure A2-31:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.4** in $CDCl_3$

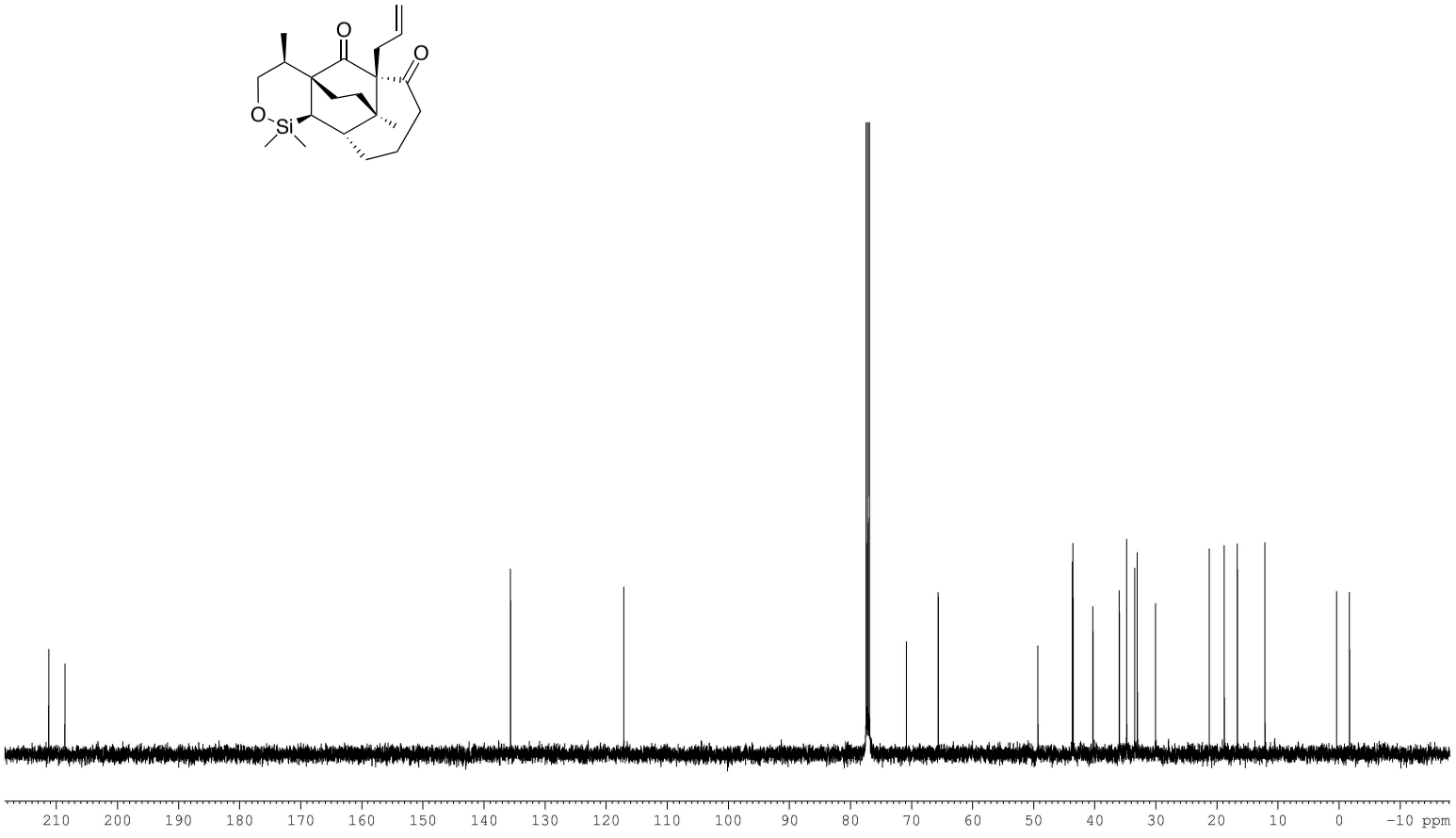



**Figure A2-32:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.4** in $CDCl_3$

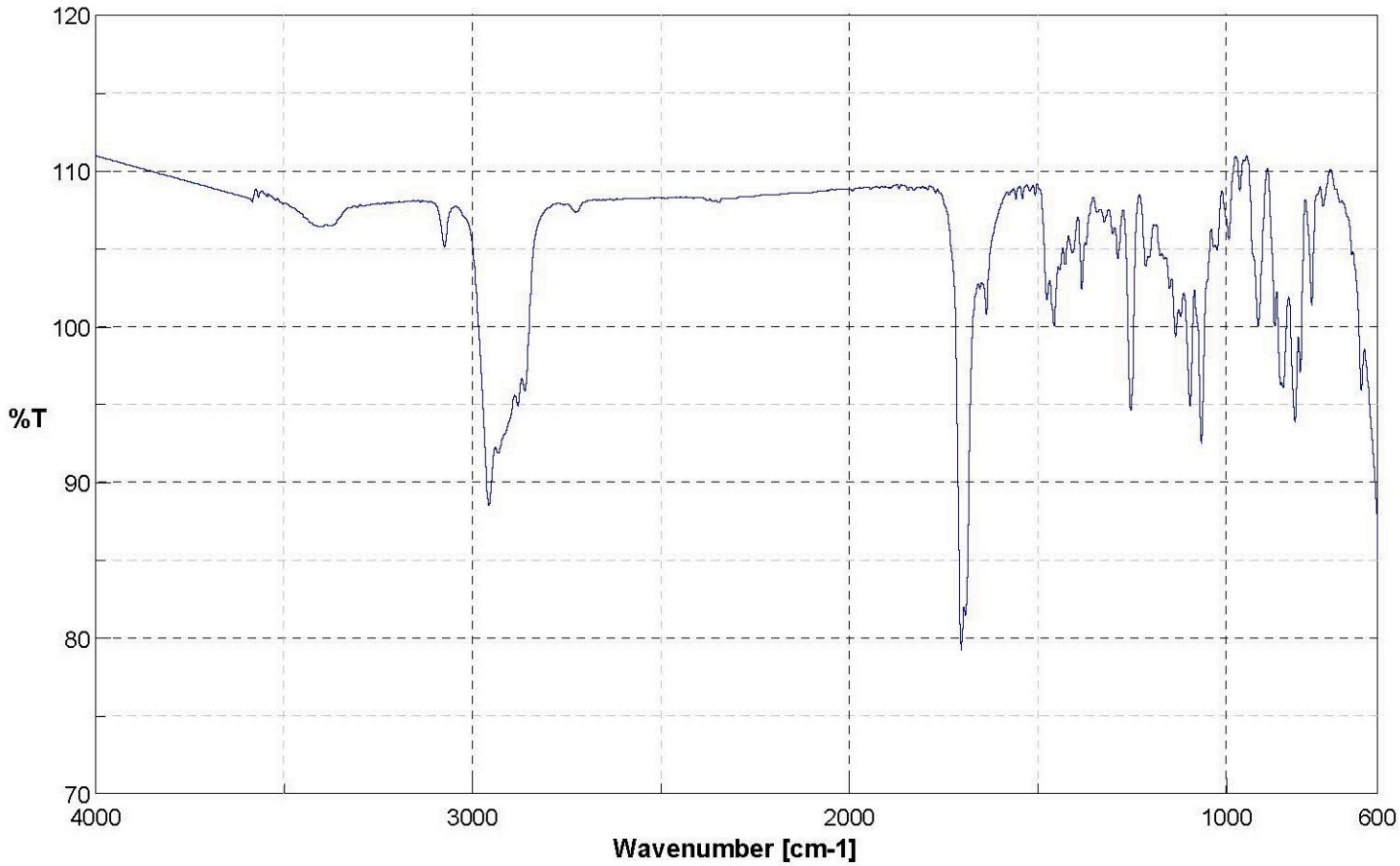



**Figure A2-33:** The Infrared Spectrum of Compound (+)-**3.4**

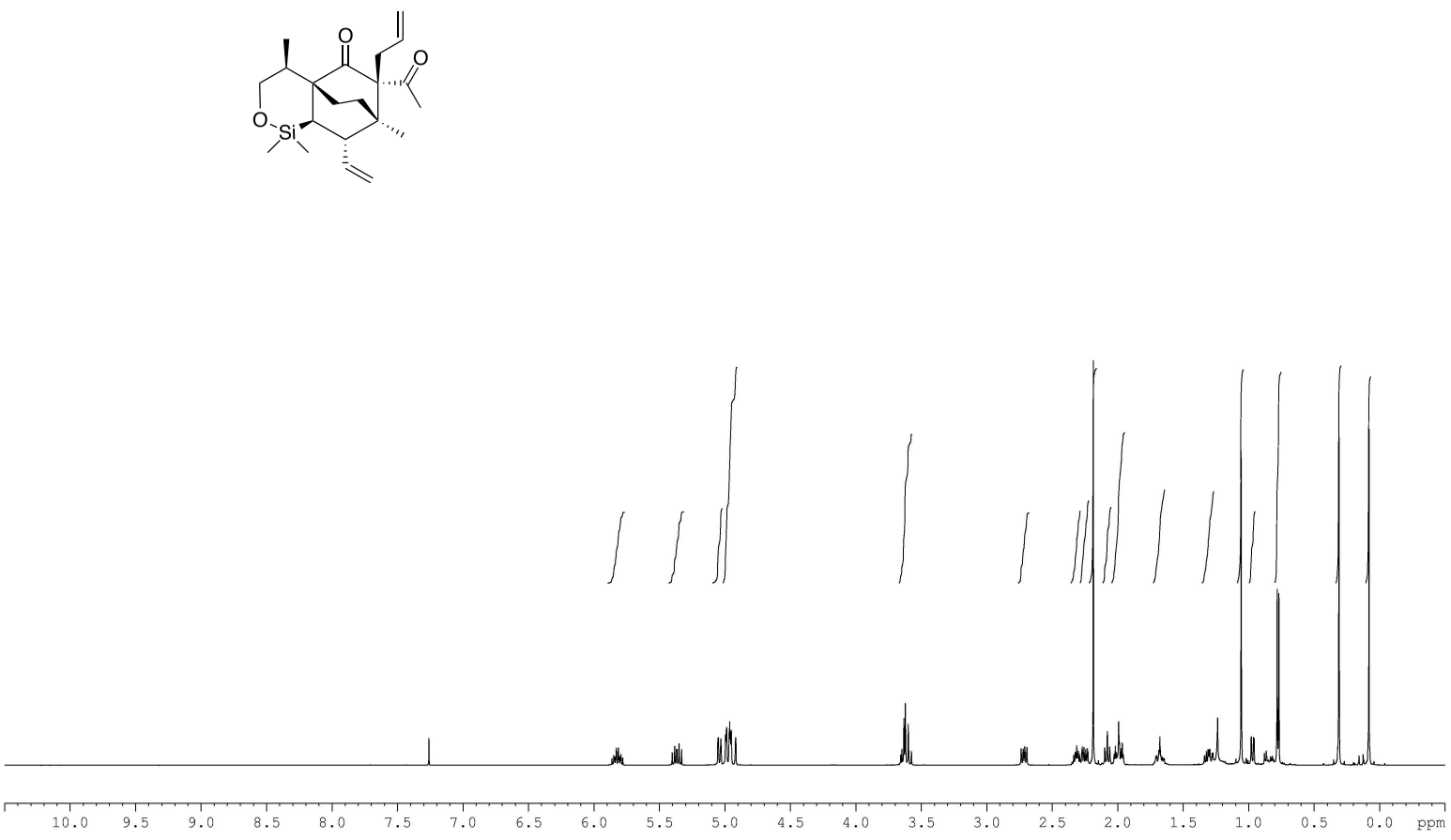



**Figure A2-34:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**3.13** in $CDCl_3$

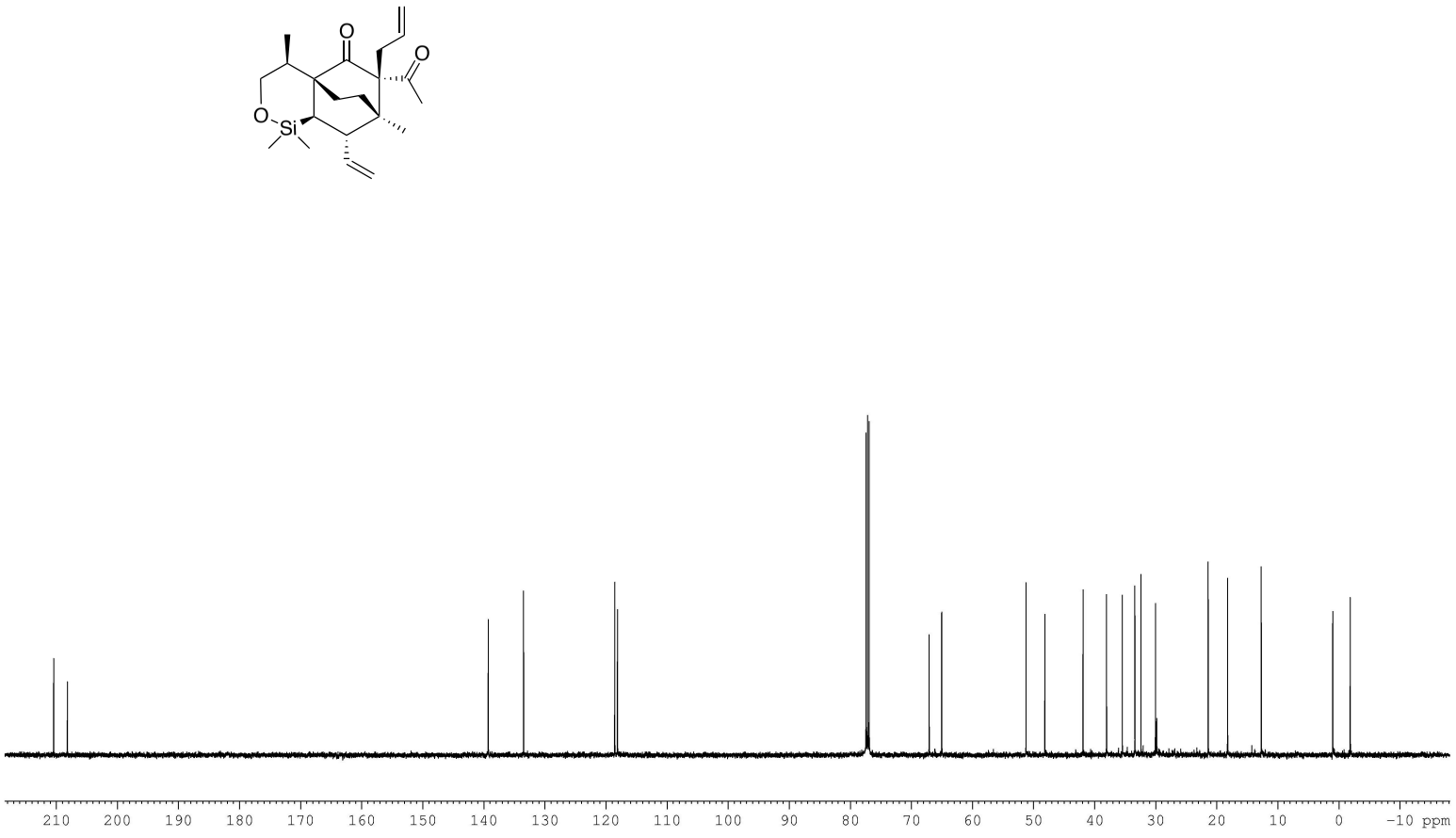



**Figure A2-35:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**3.13** in $CDCl_3$

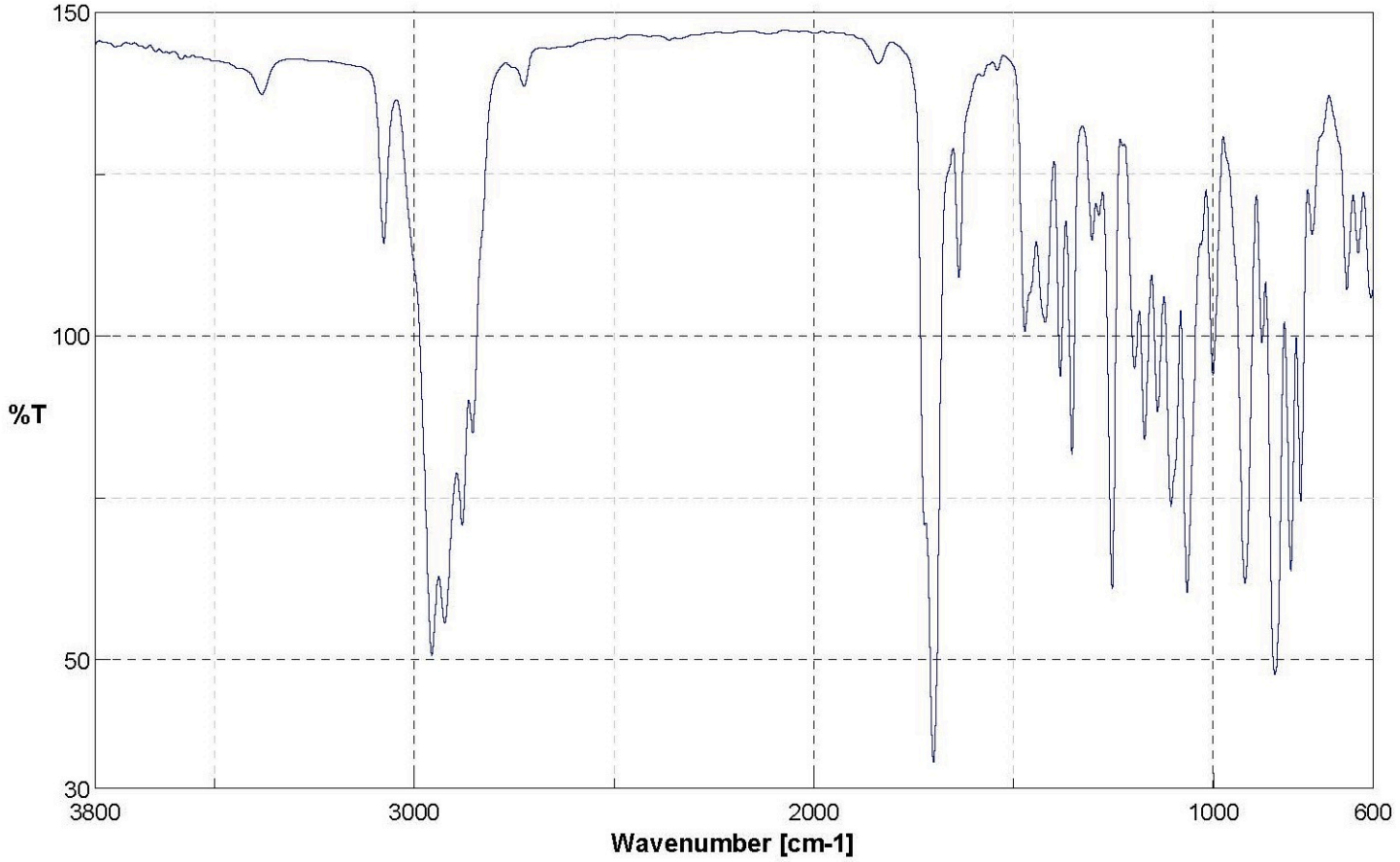



**Figure A2-36:** The Infrared Spectrum of Compound (–)-**3.13**

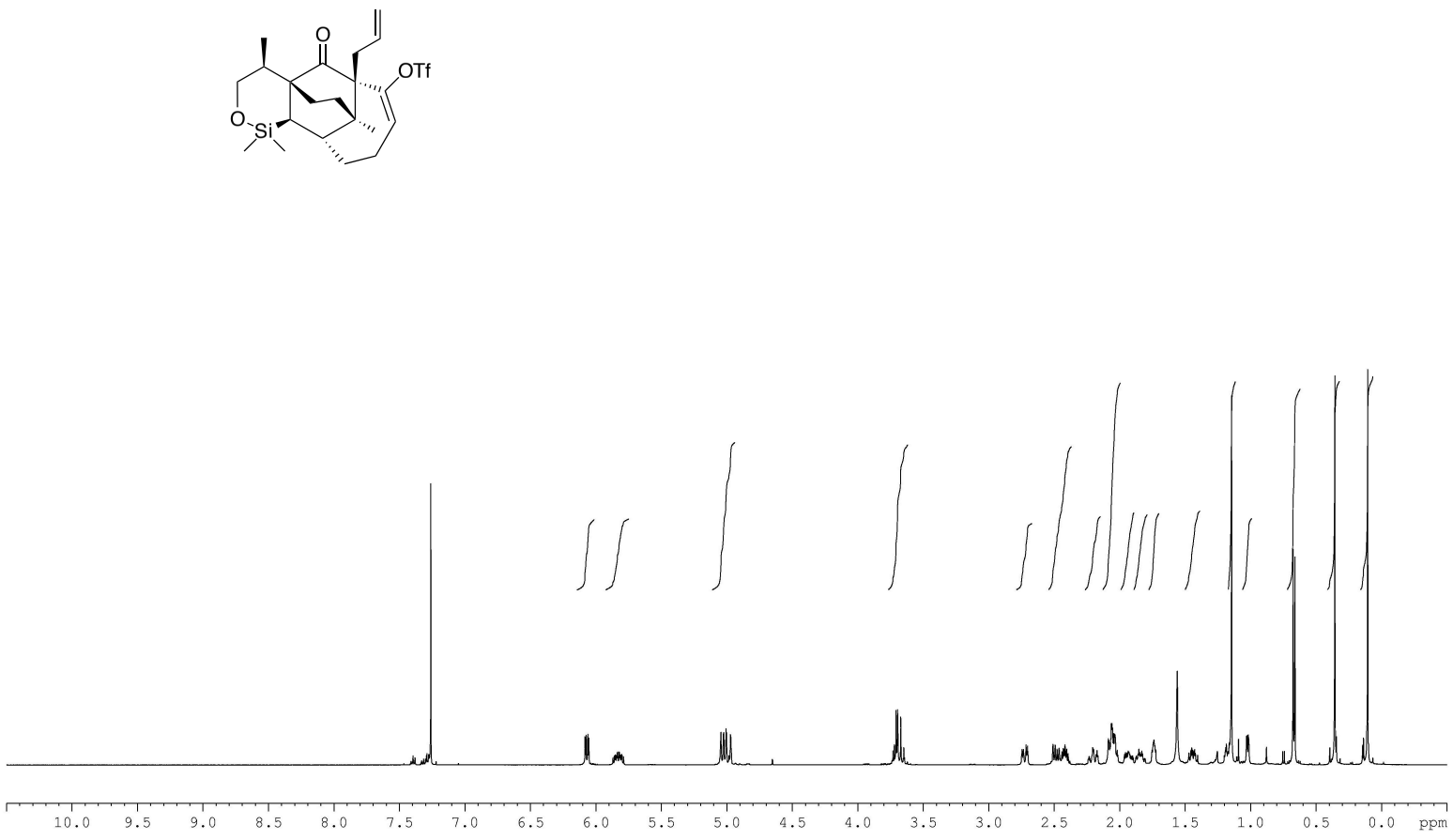



**Figure A2-37:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.19** in $CDCl_3$

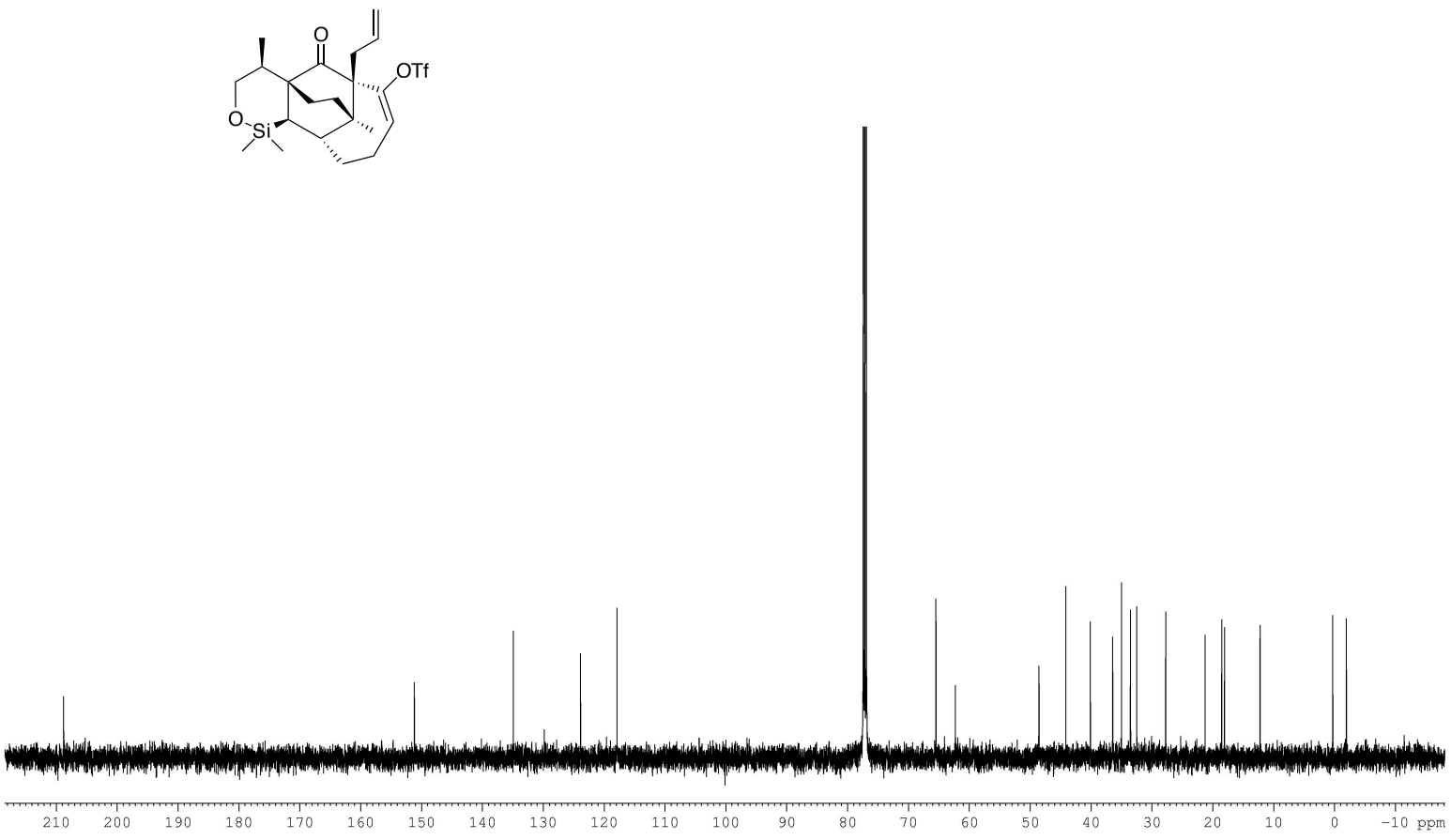



**Figure A2-38:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.19** in $CDCl_3$

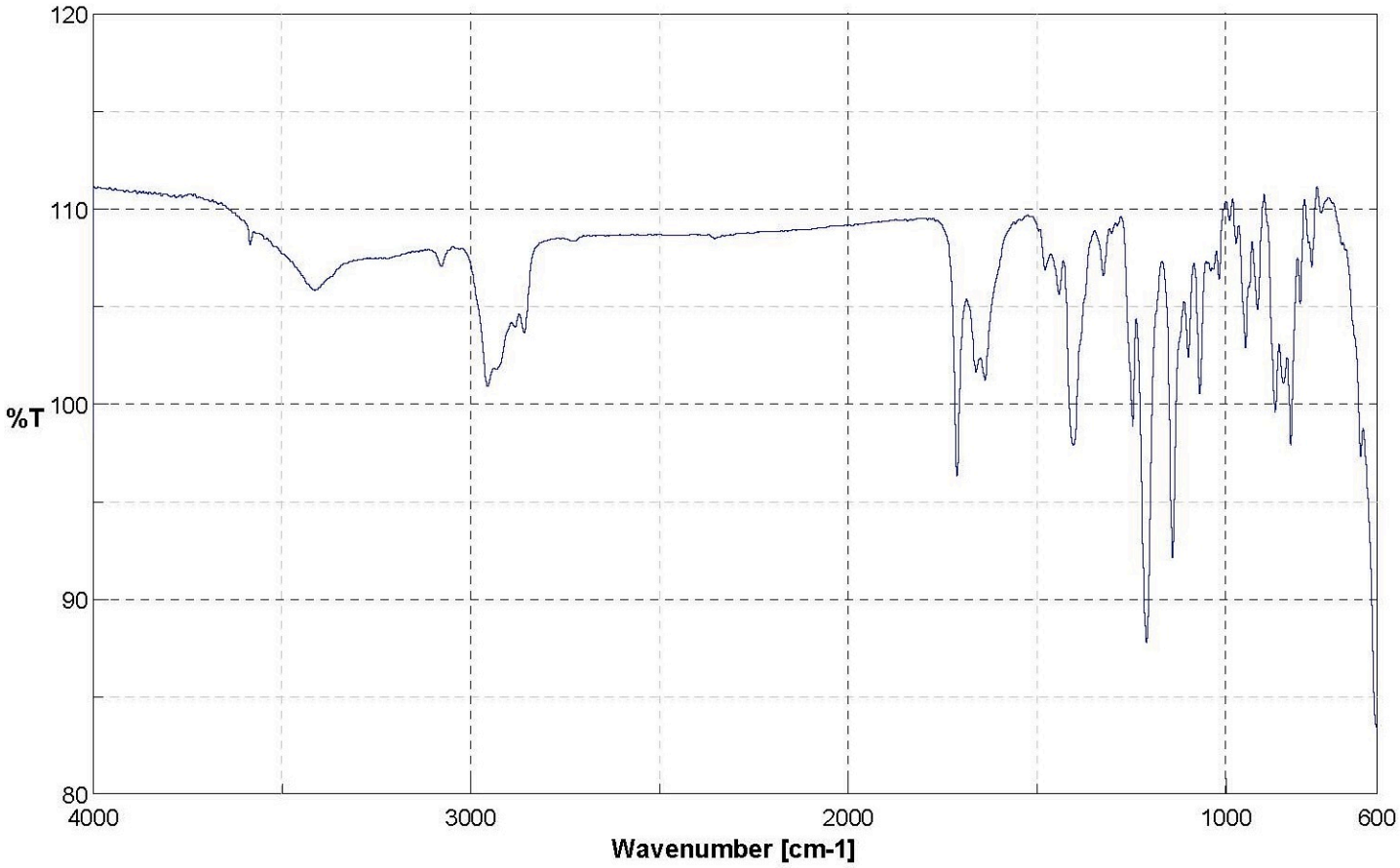



**Figure A2-39:** The Infrared Spectrum of Compound (+)-**3.19**

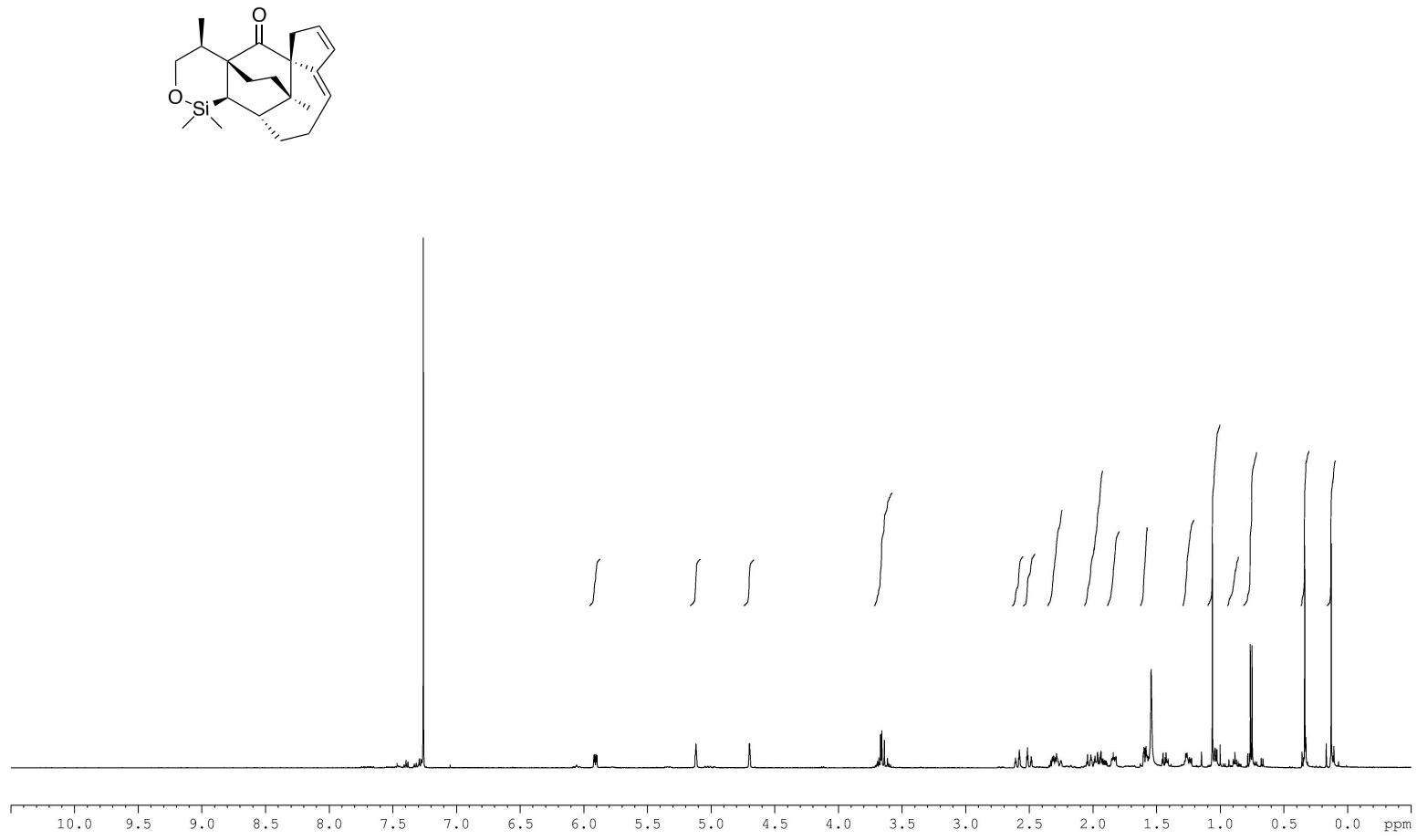



**Figure A2-40:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.21** in $CDCl_3$

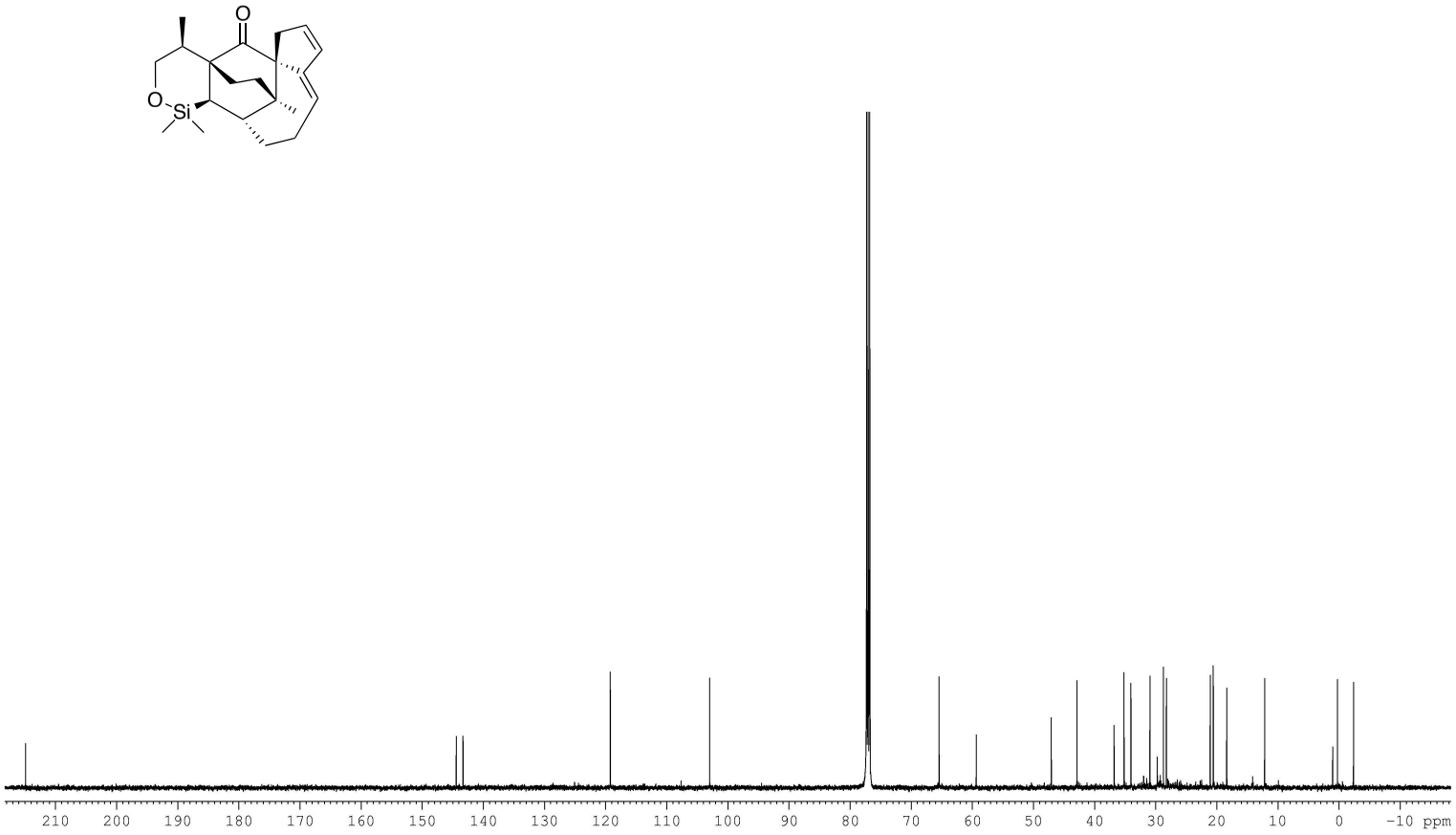



**Figure A2-41:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.21** in $CDCl_3$

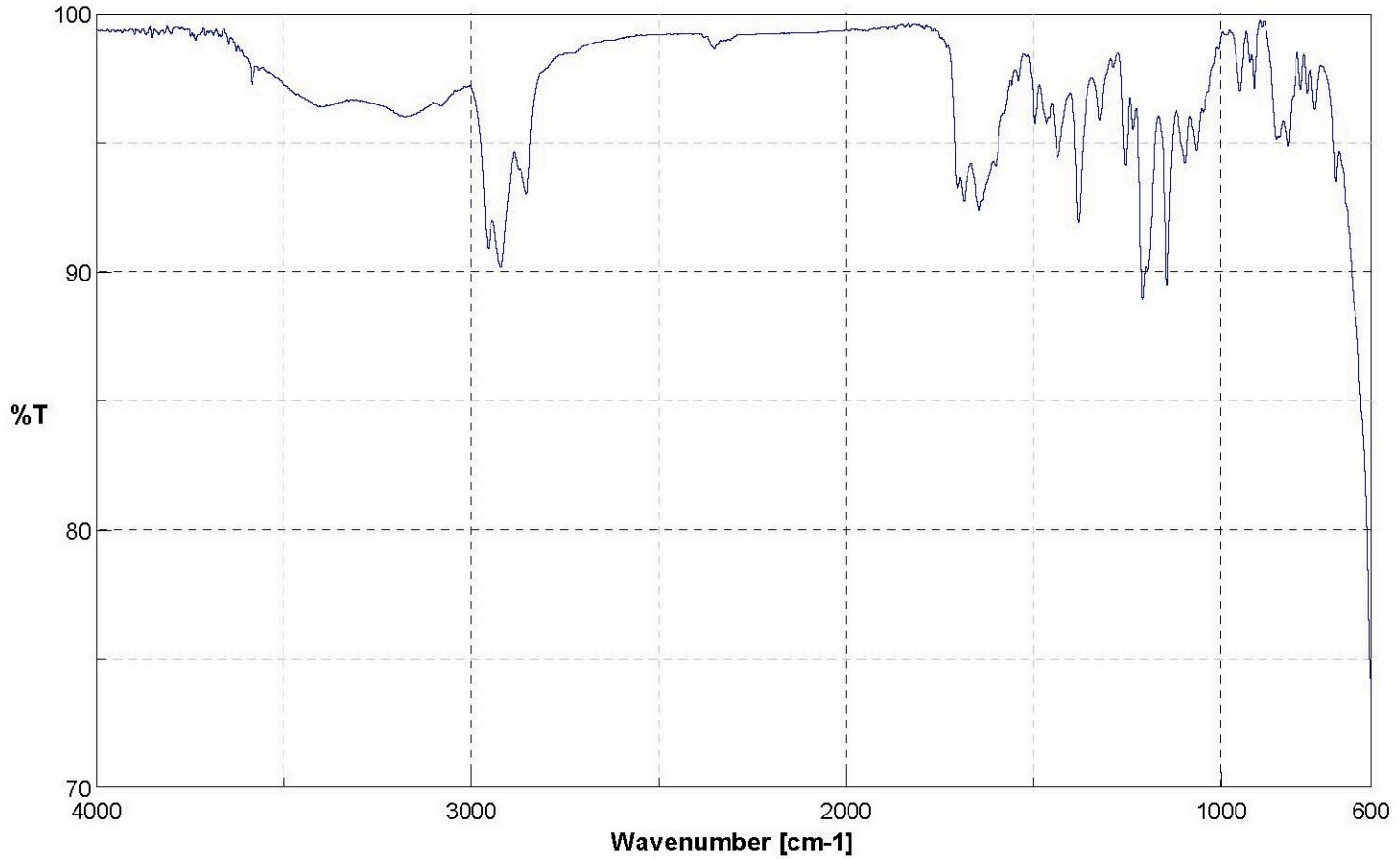



**Figure A2-42:** The Infrared Spectrum of Compound (+)-**3.21**

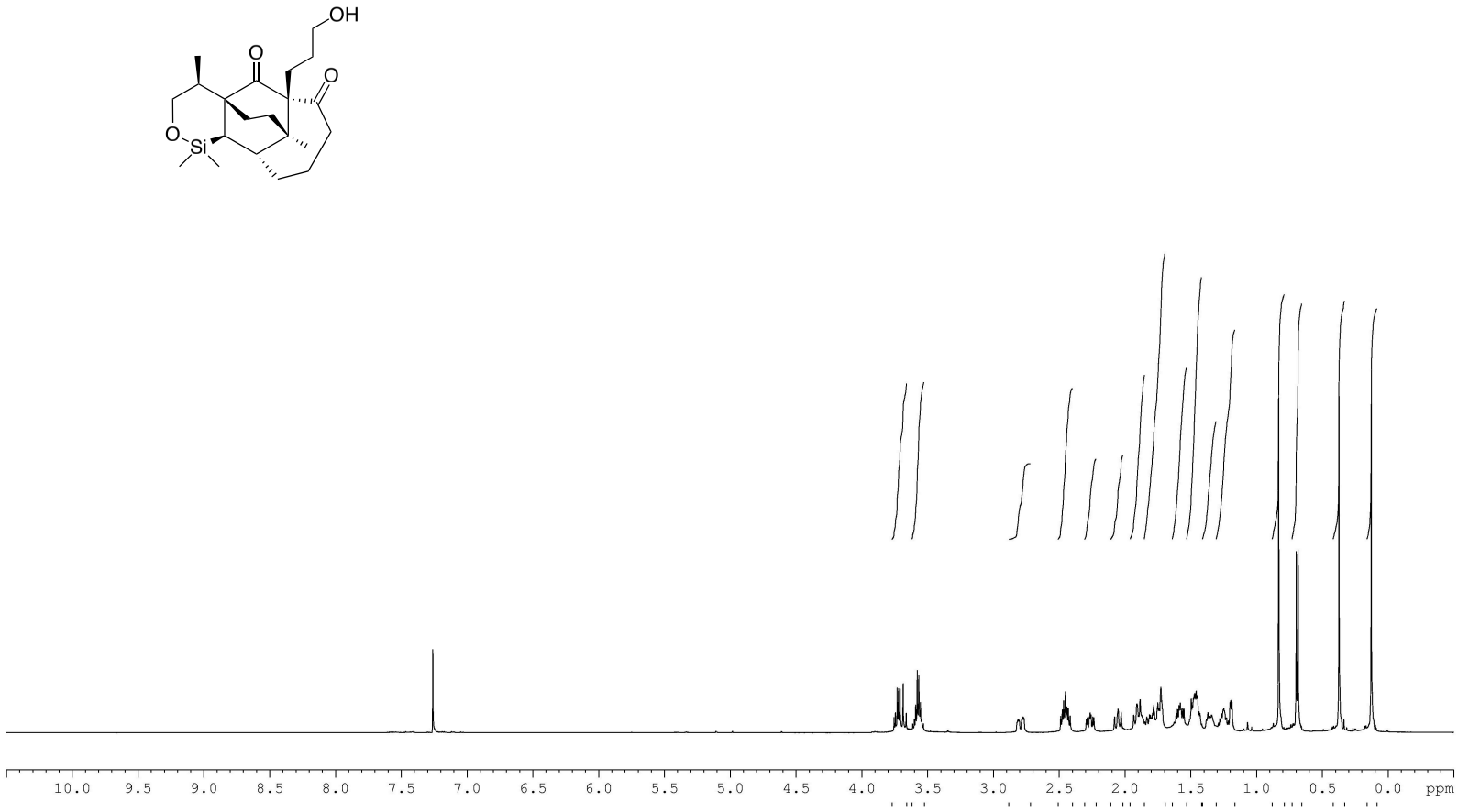



**Figure A2-43:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.22** in $CDCl_3$

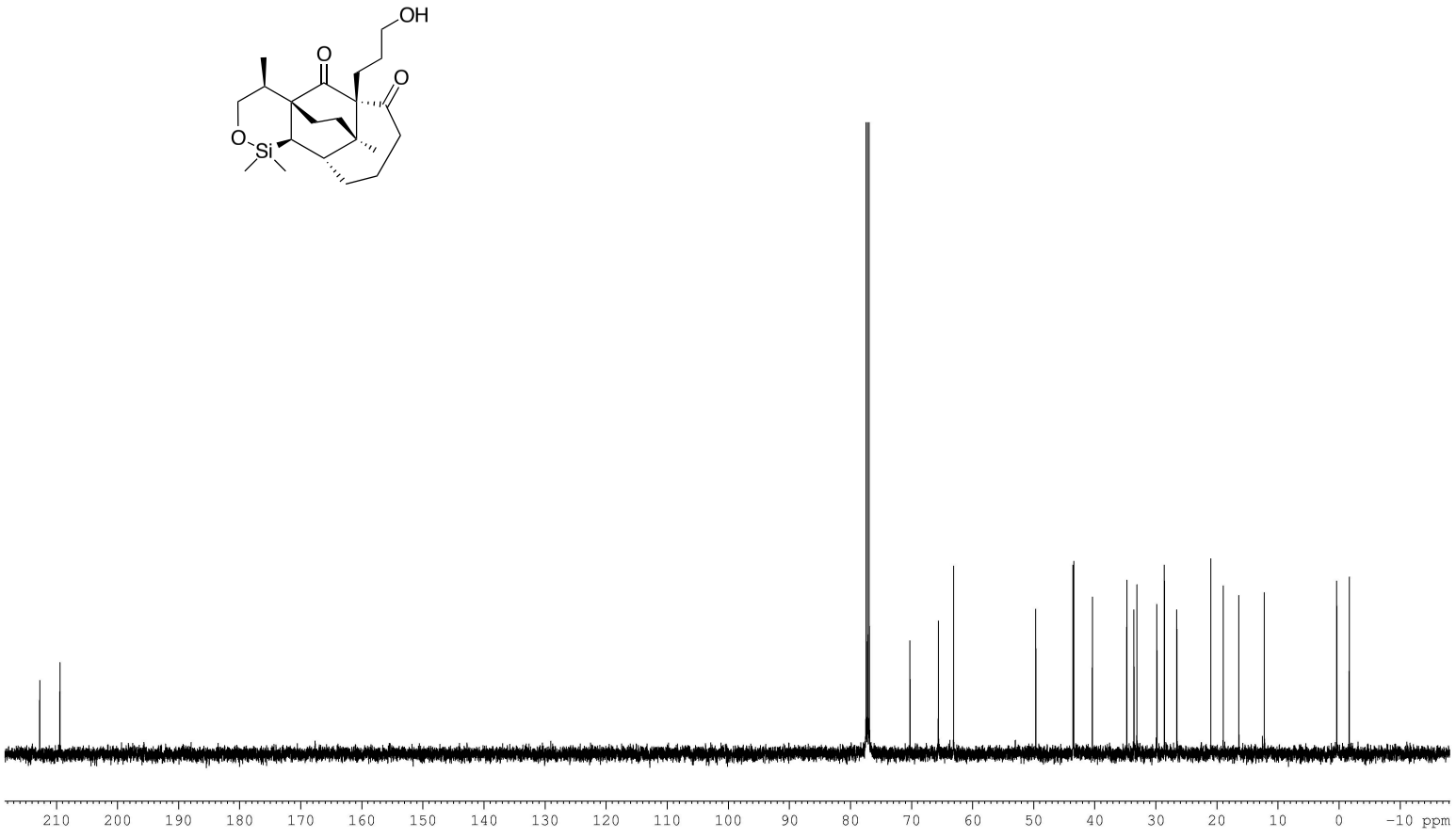



**Figure A2-44:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.22** in $CDCl_3$

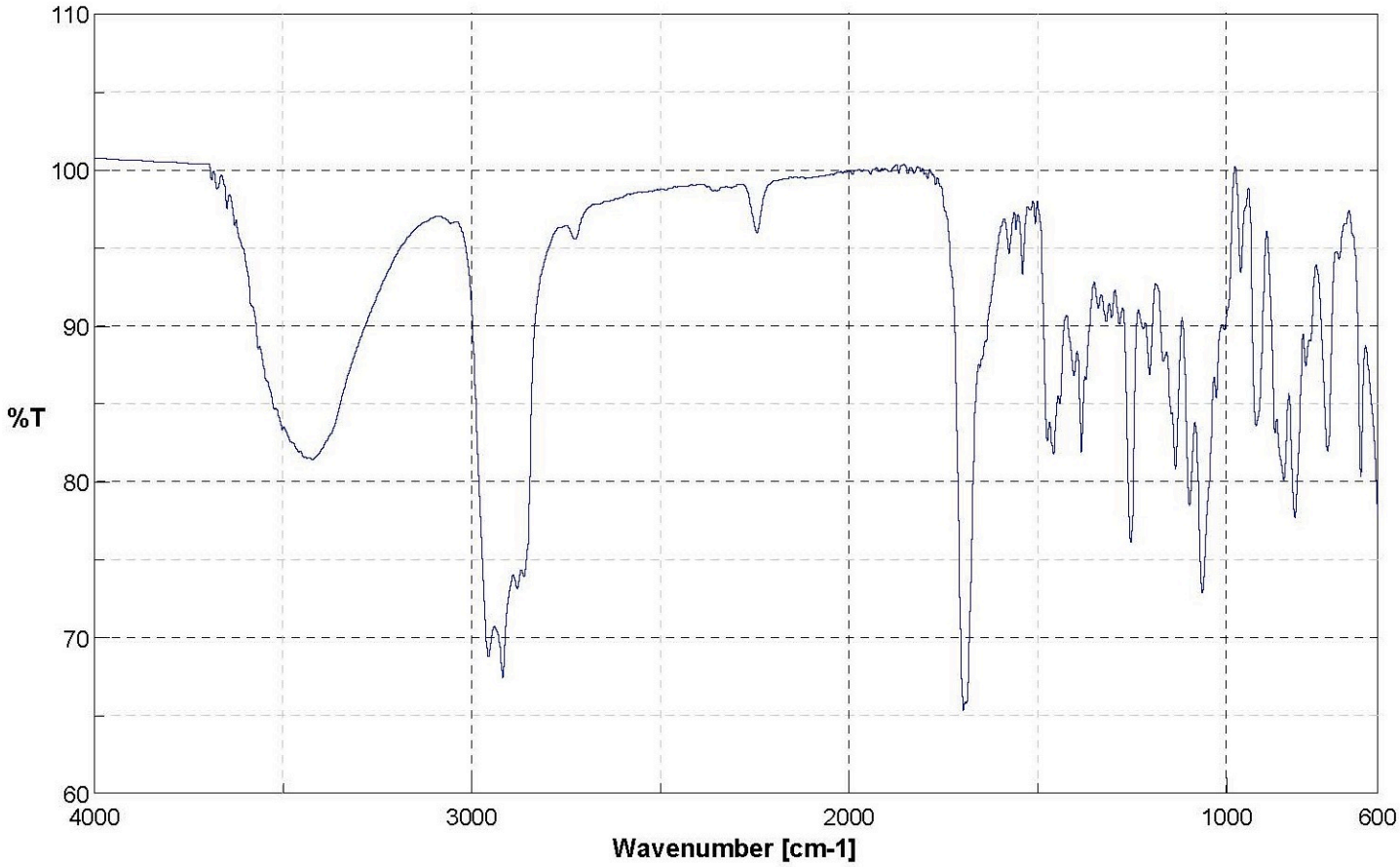



**Figure A2-45:** The Infrared Spectrum of Compound (+)-**3.22**

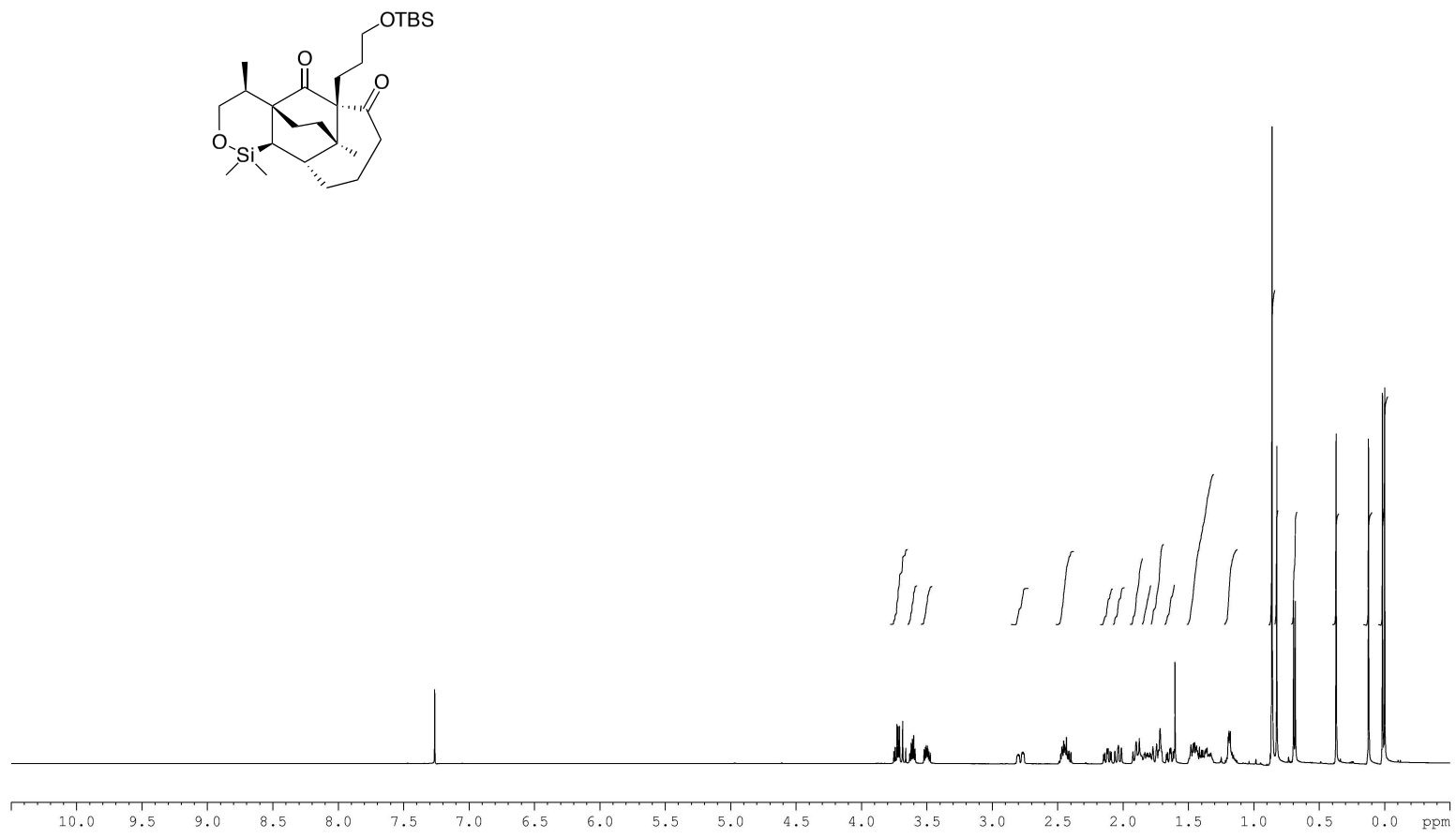



**Figure A2-46:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.23** in $CDCl_3$

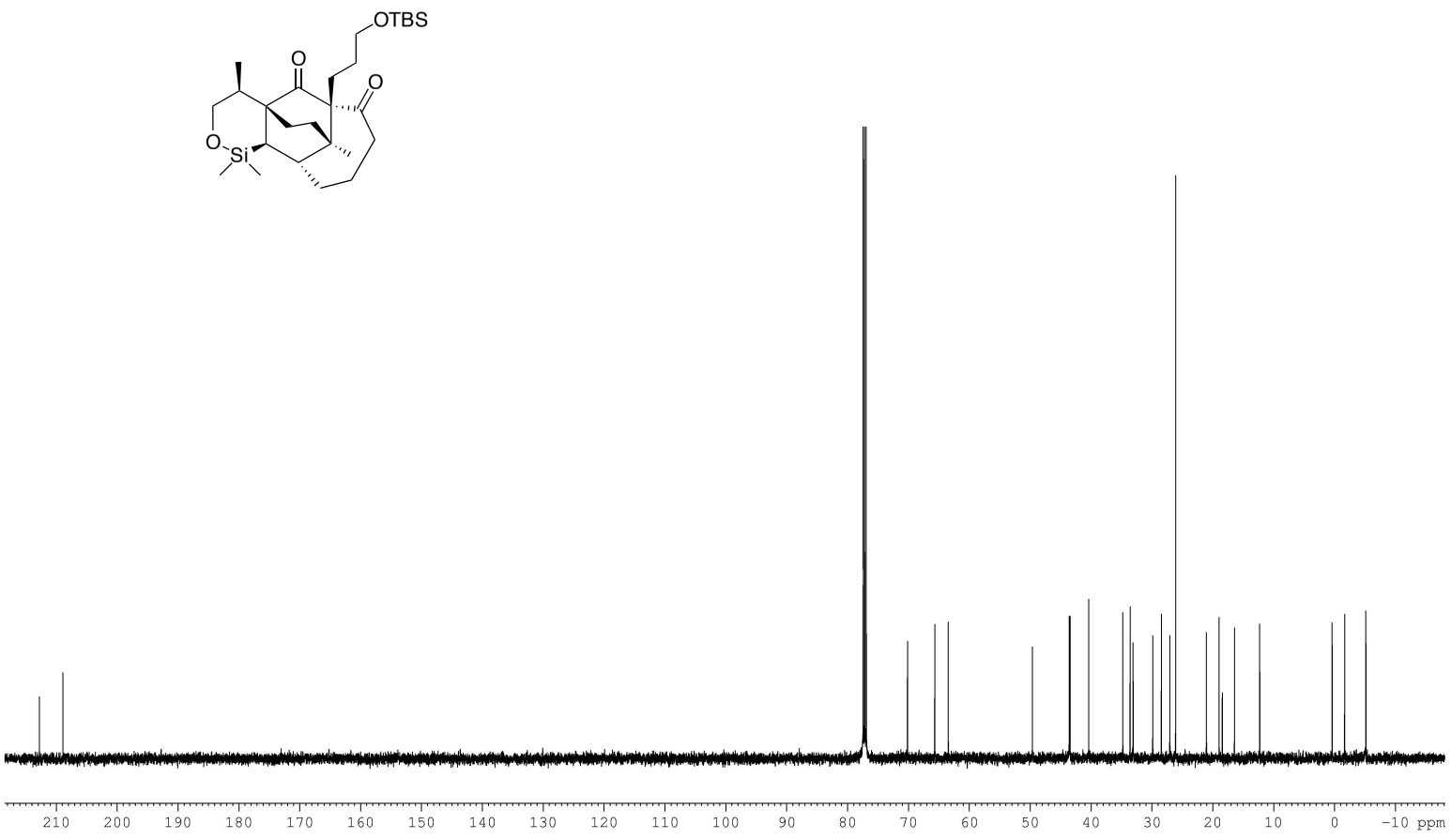



**Figure A2-47:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.23** in $CDCl_3$

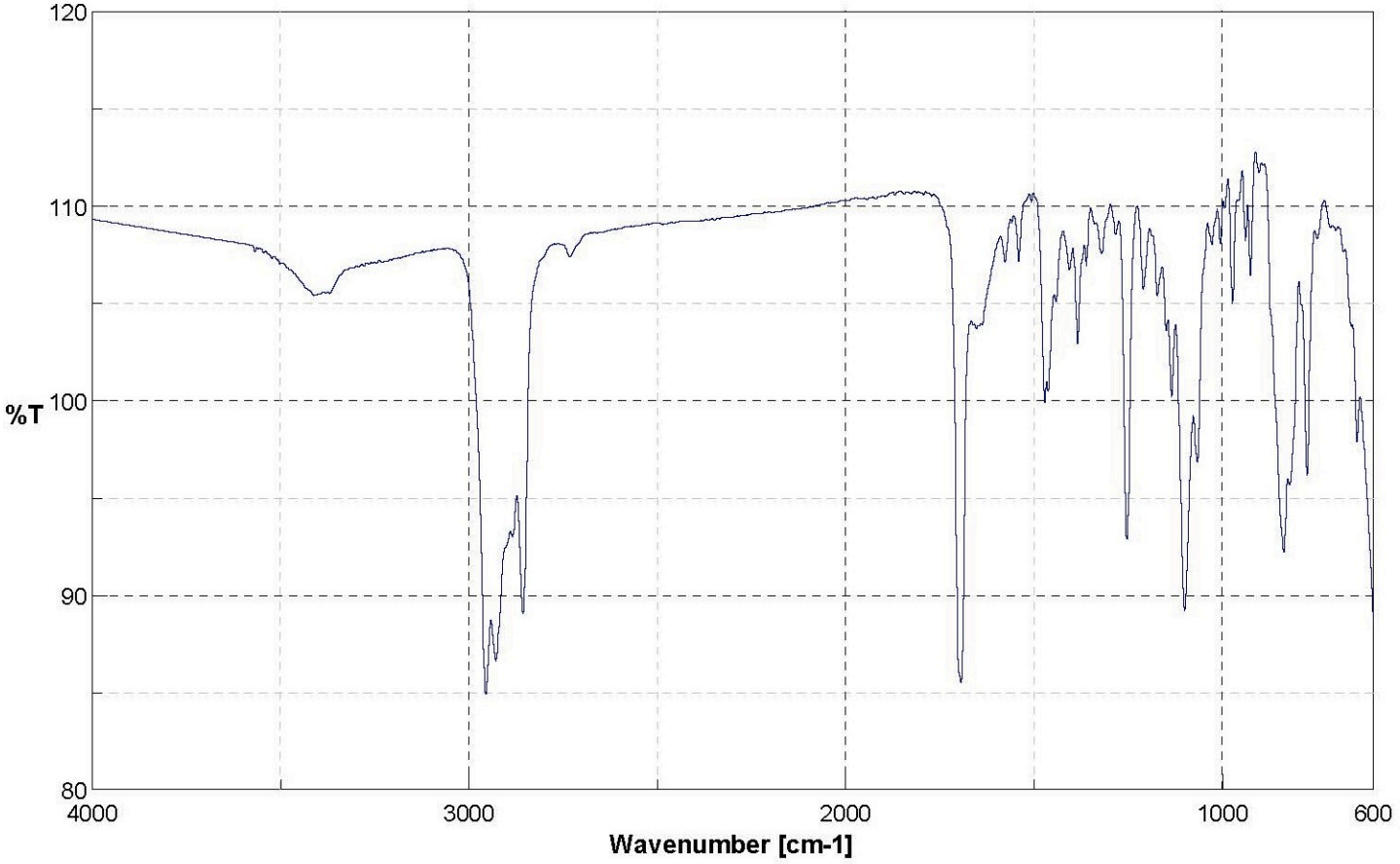



**Figure A2-48:** The Infrared Spectrum of Compound (+)-**3.23**

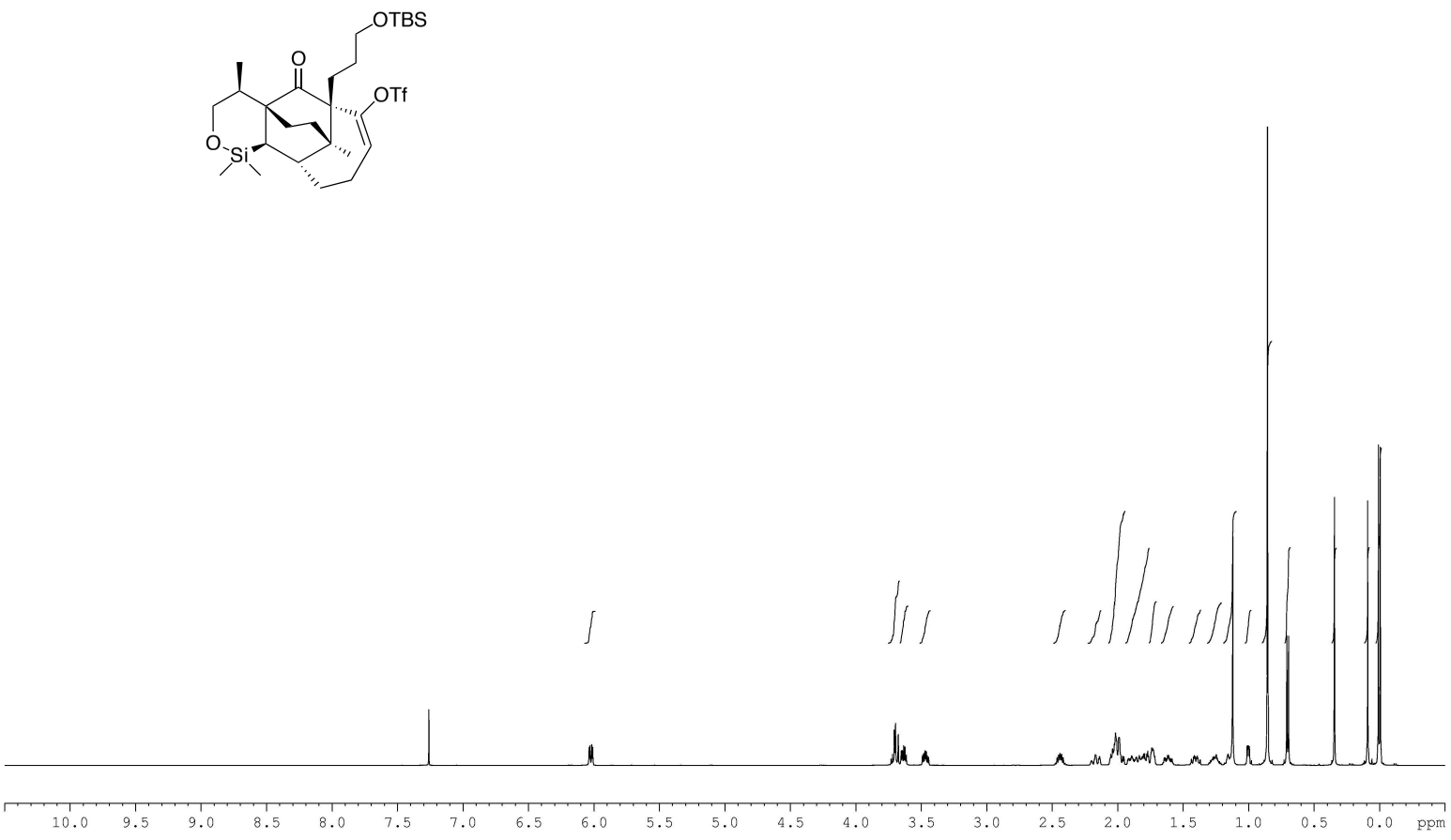



**Figure A2-49:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.24** in $CDCl_3$

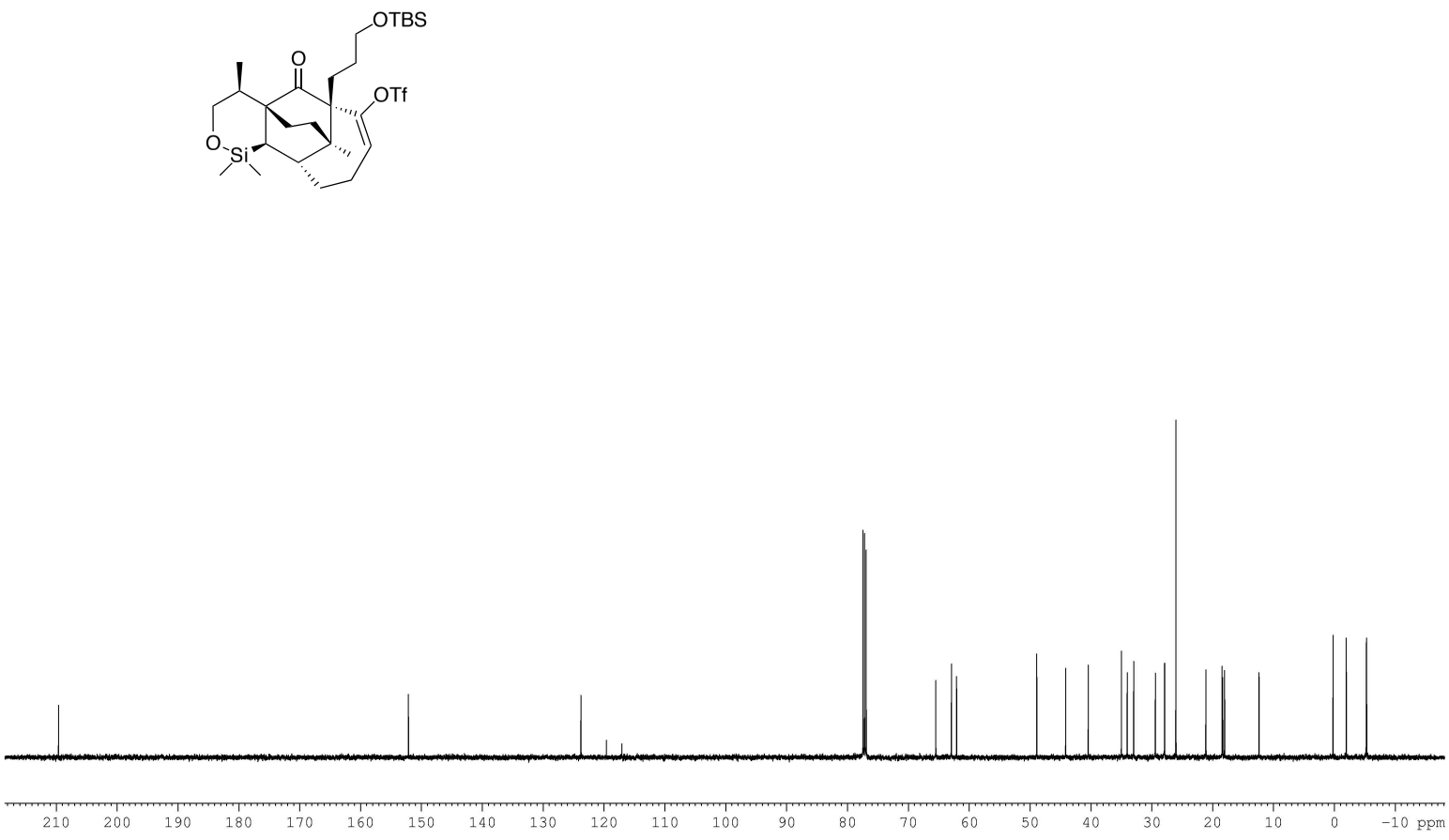



**Figure A2-50:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.24** in $CDCl_3$

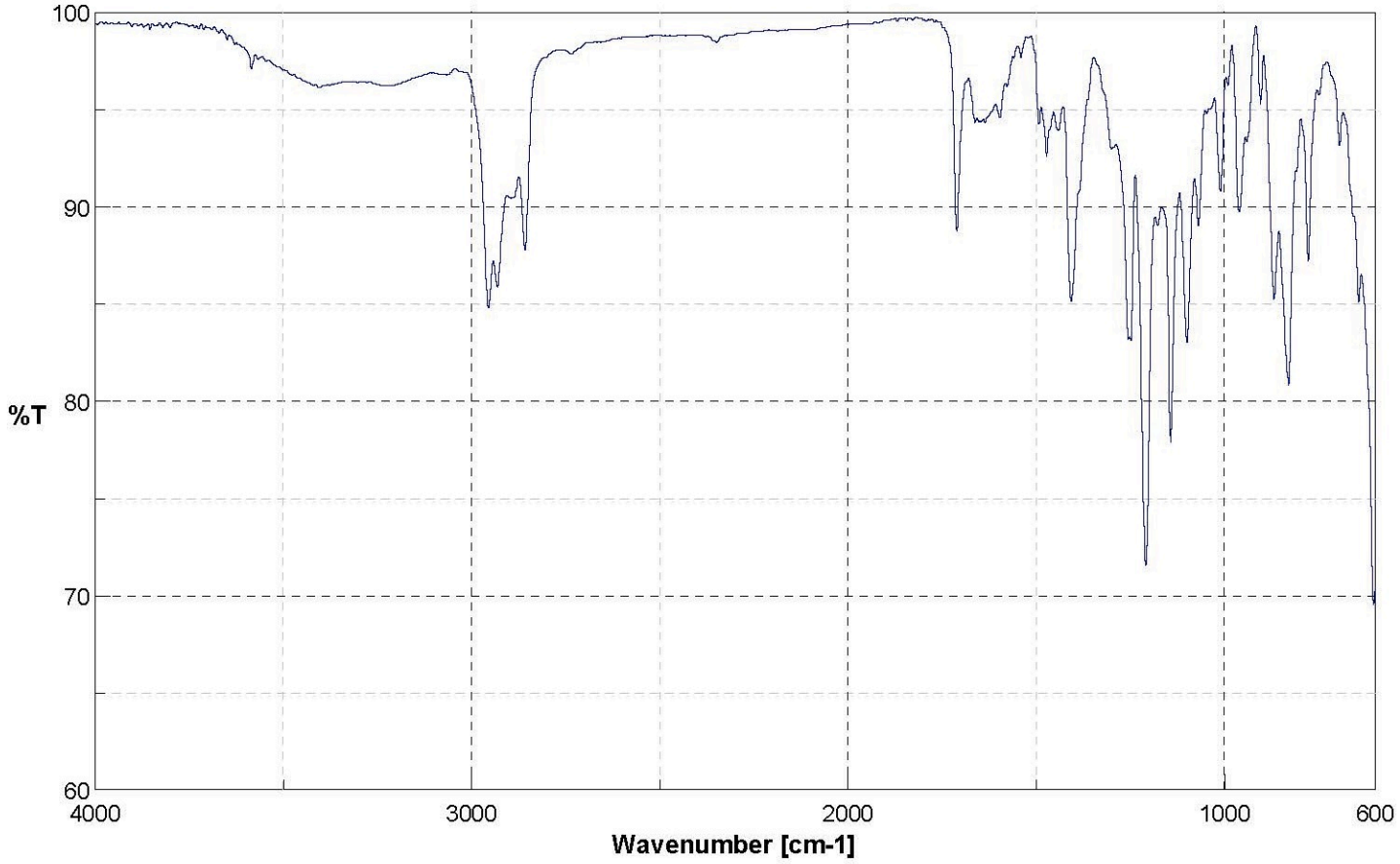



**Figure A2-51:** The Infrared Spectrum of Compound (+)-**3.24**

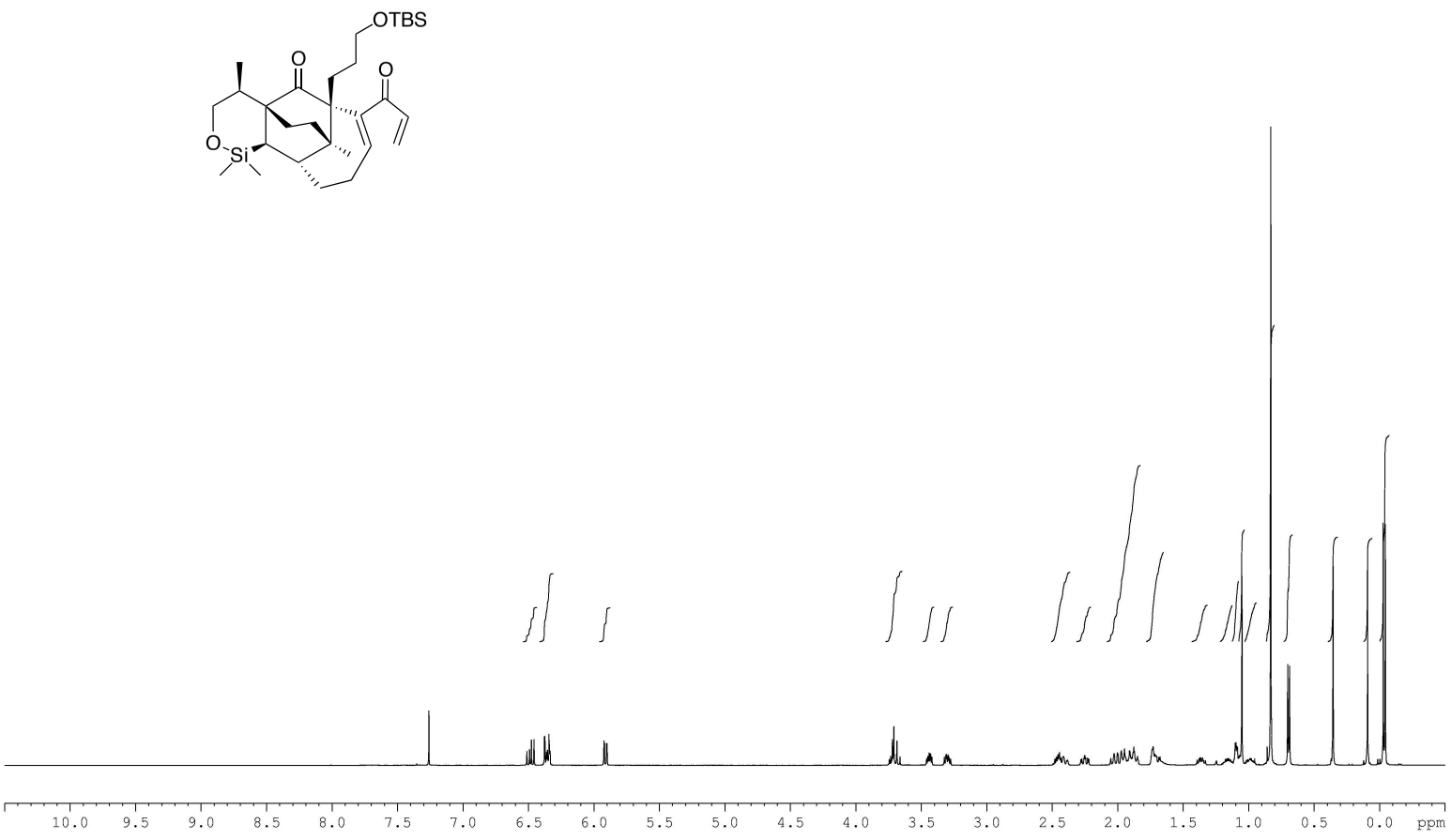



**Figure A2-52:** The 500 MHz $^{1}$H NMR Spectrum of (+)-**3.25** in $CDCl_3$

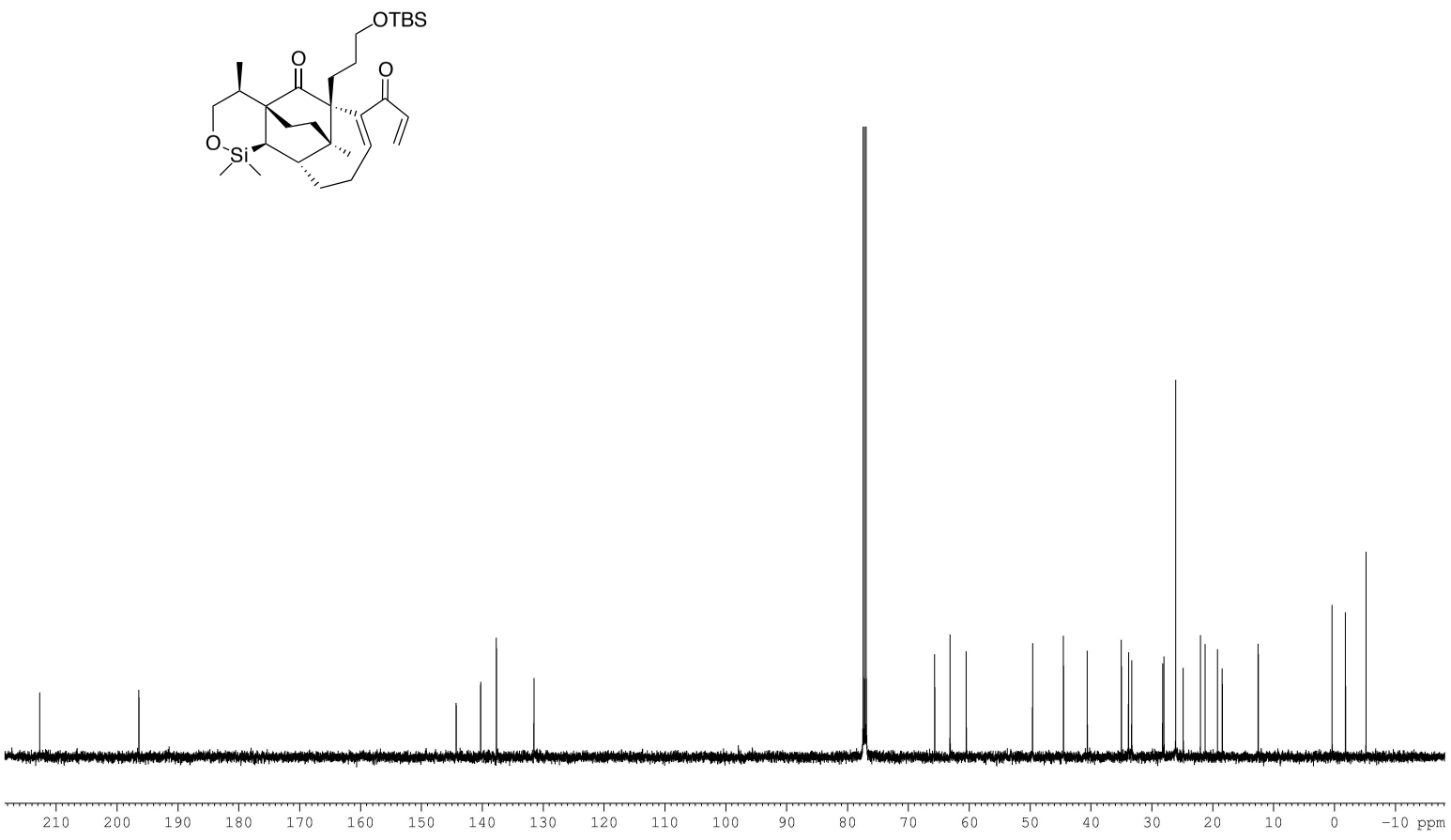



**Figure A2-53:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.25** in $CDCl_3$

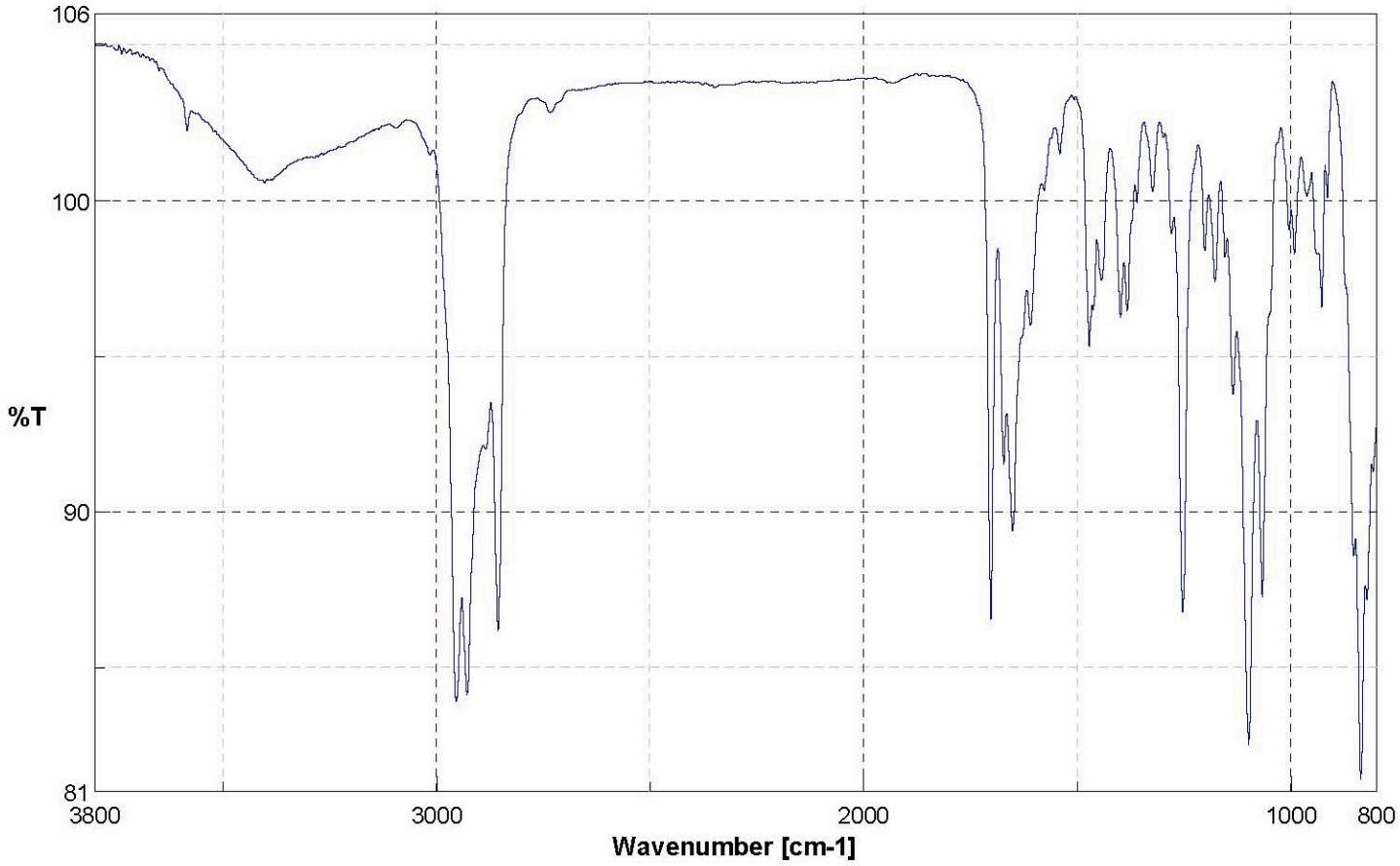



**Figure A2-54:** The Infrared Spectrum of Compound (+)-**3.25**

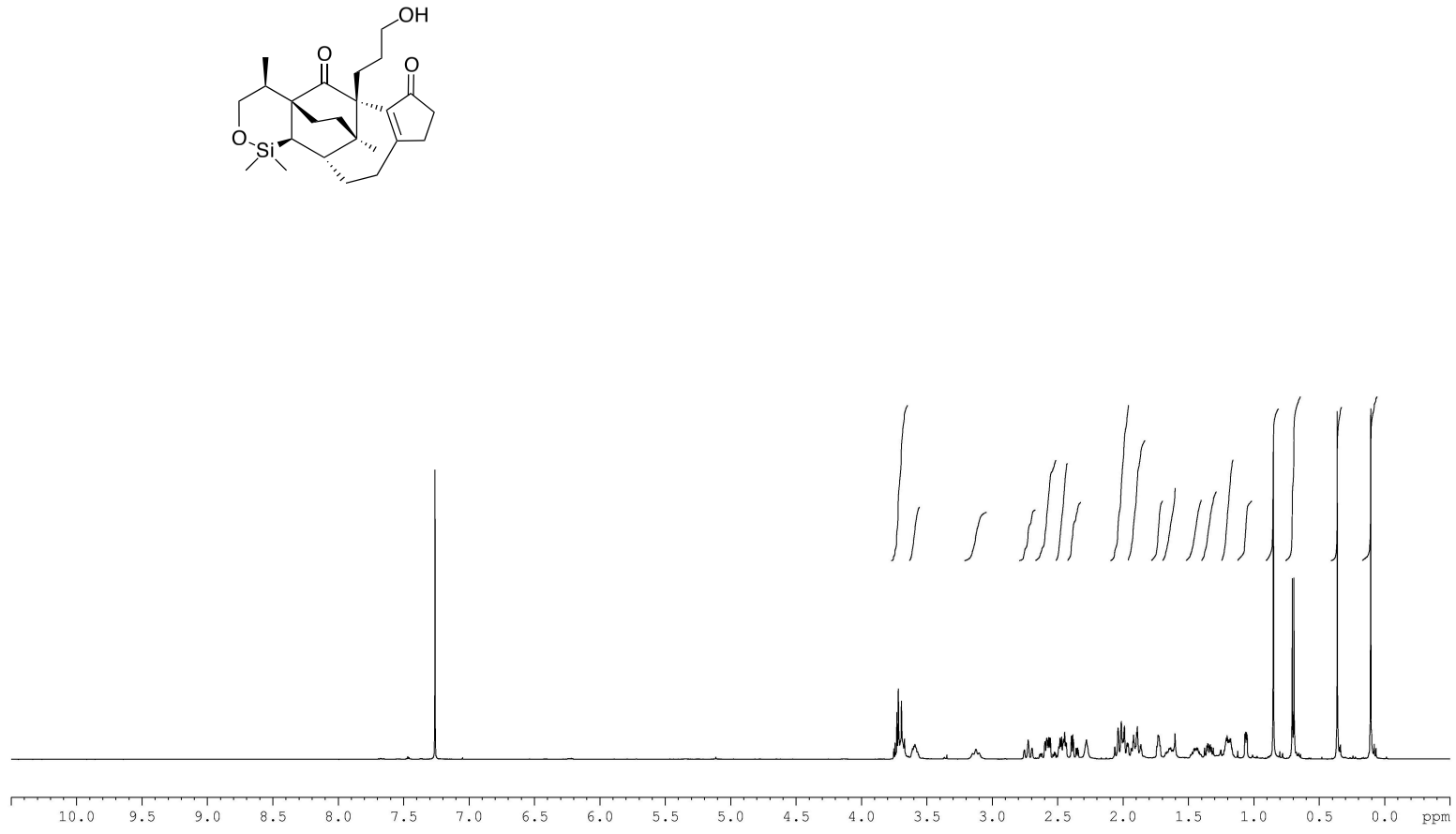



**Figure A2-55:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.26** in $CDCl_3$

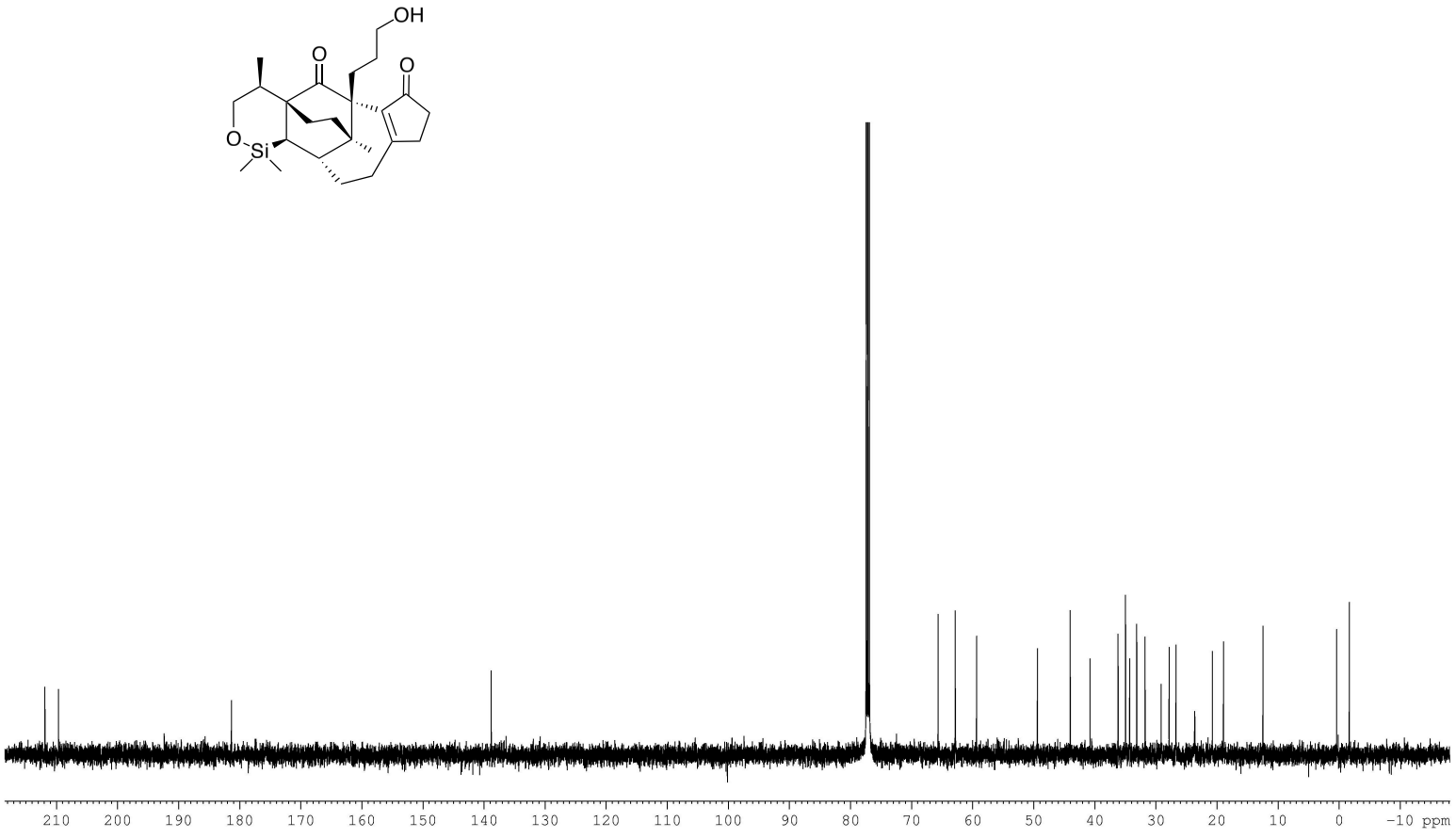



**Figure A2-56:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.26** in $CDCl_3$

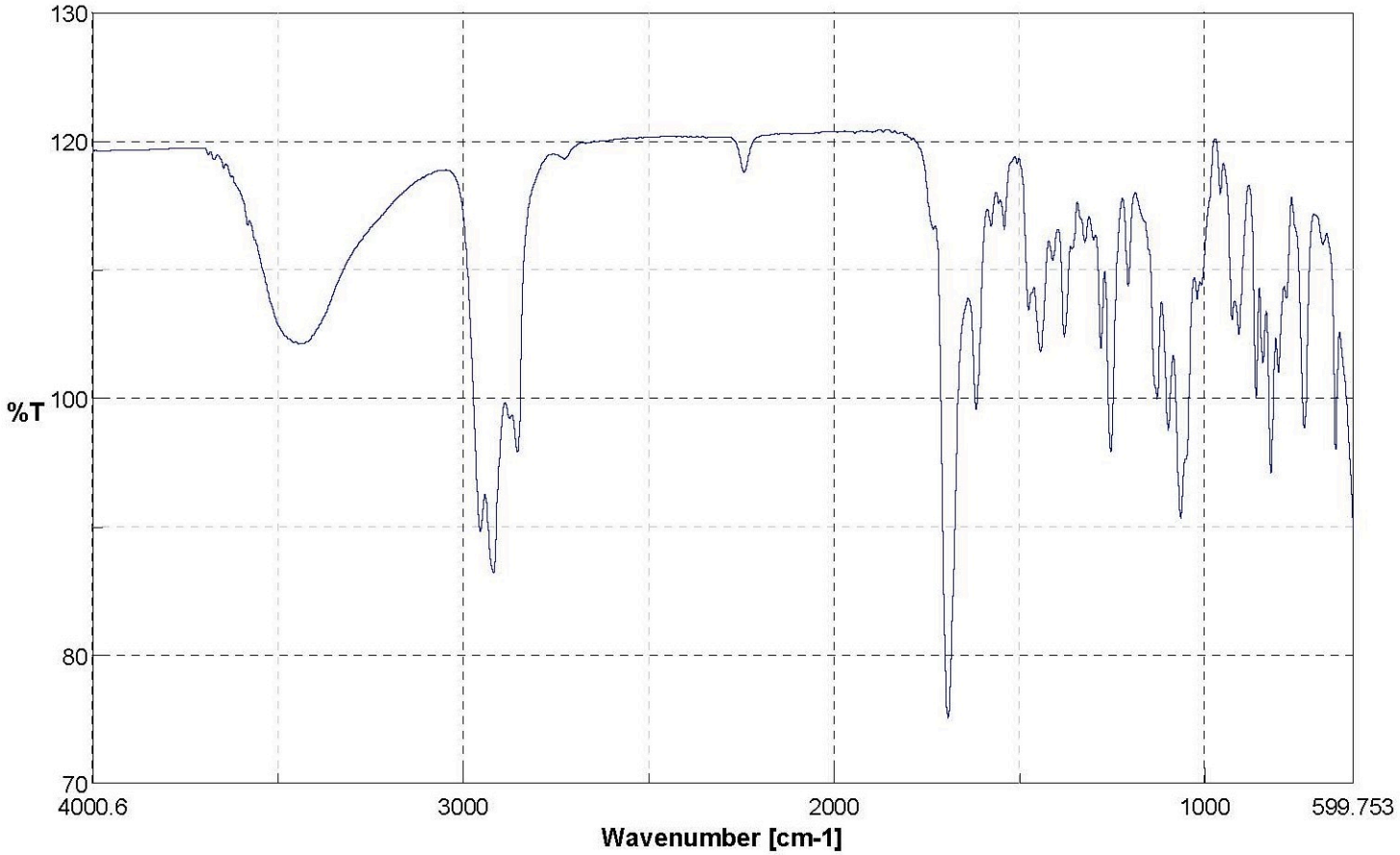



**Figure A2-57:** The Infrared Spectrum of Compound (+)-**3.26**

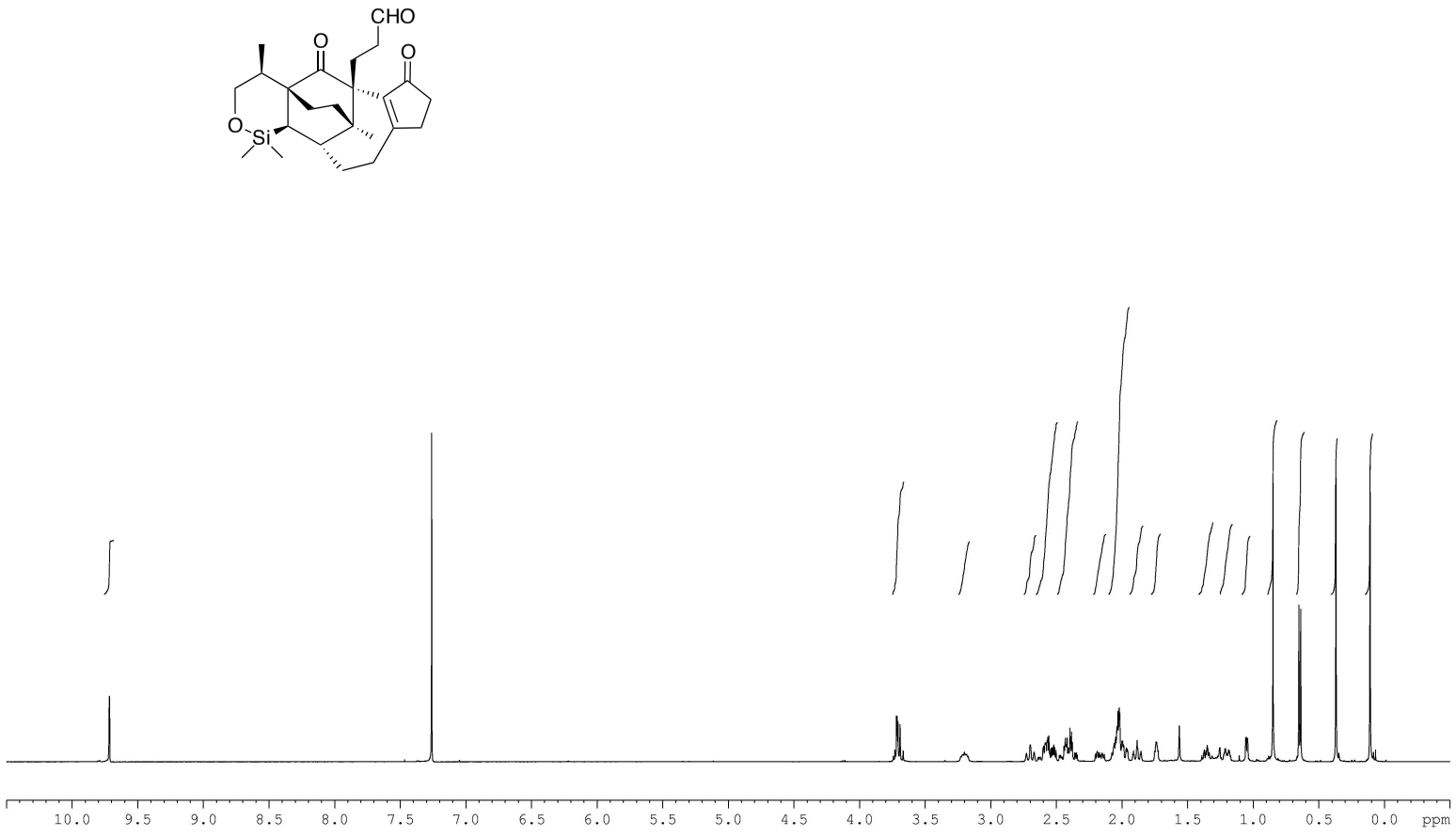



**Figure A2-58:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.27** in $CDCl_3$

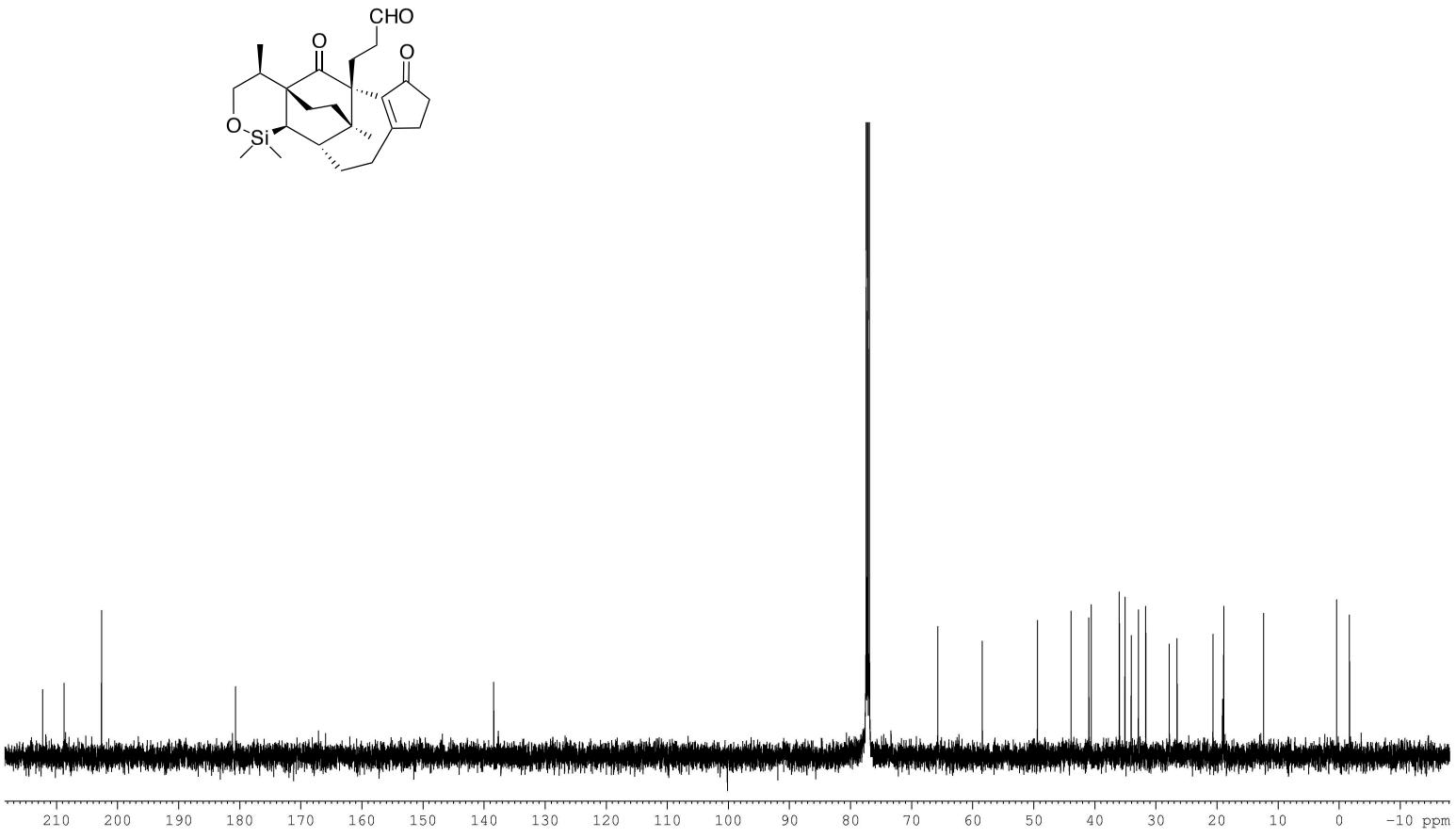



**Figure A2-59:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.27** in $CDCl_3$

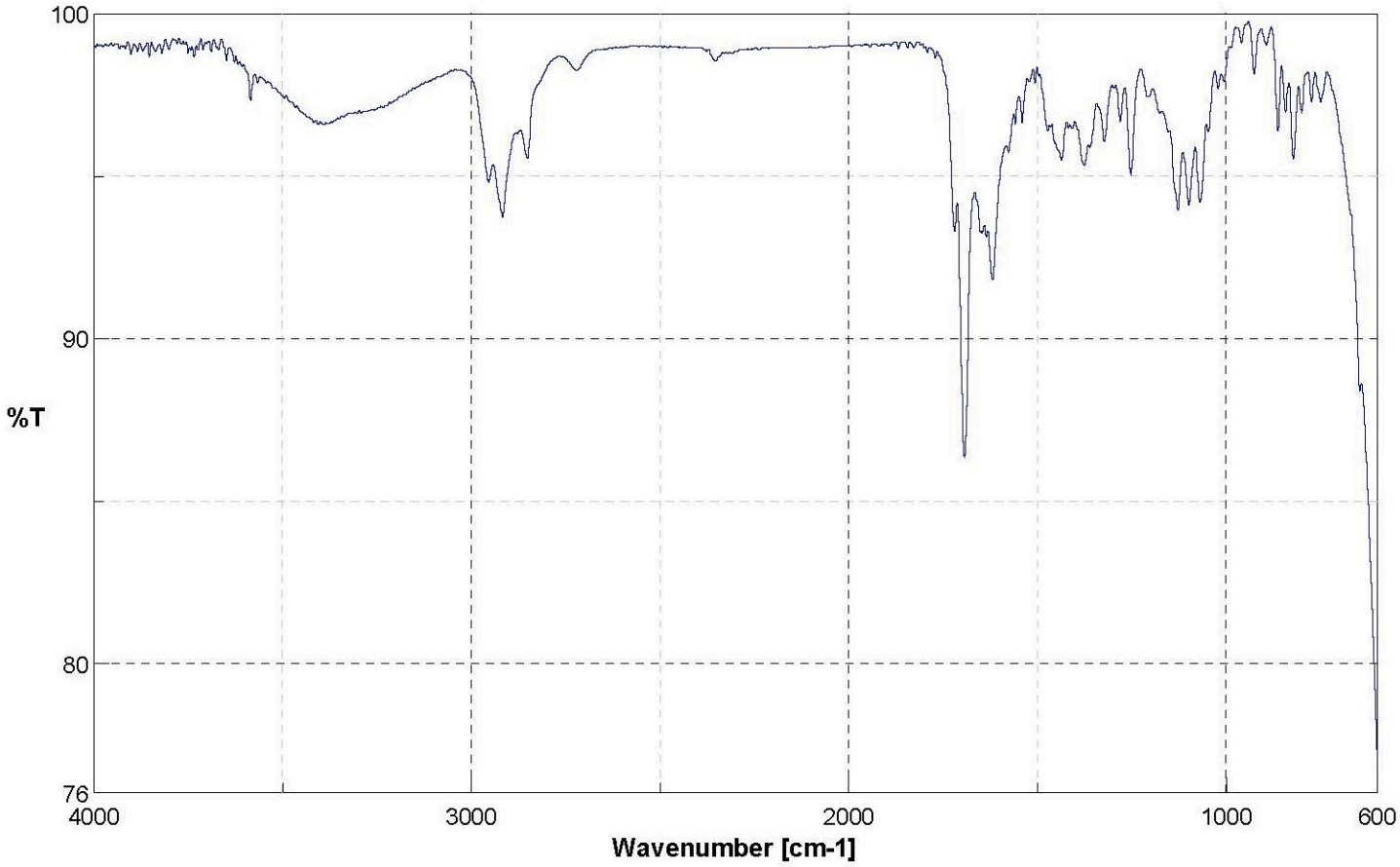



**Figure A2-60:** The Infrared Spectrum of Compound (+)-**3.27**

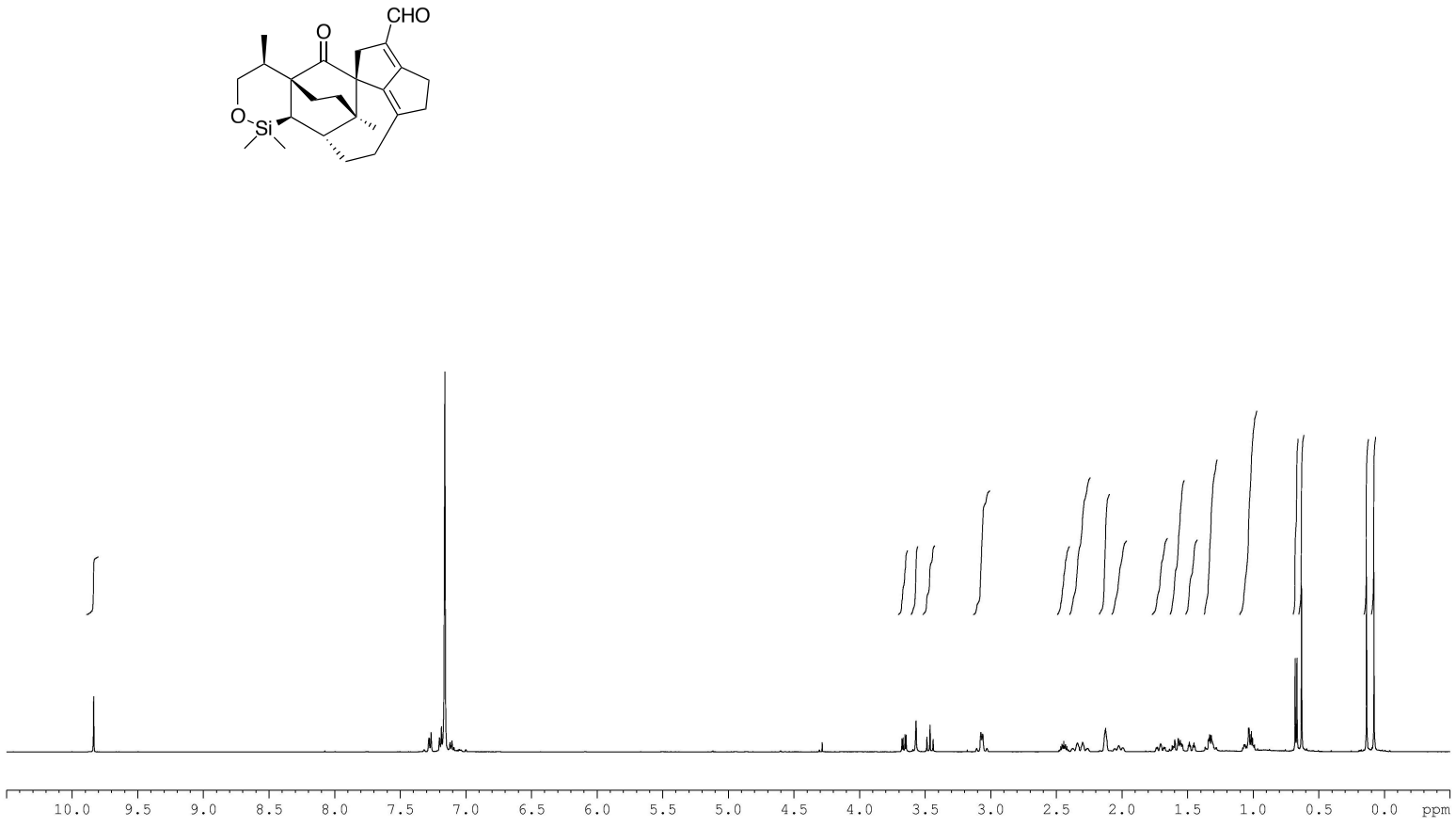



**Figure A2-61:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.28** in $C_6D_6$

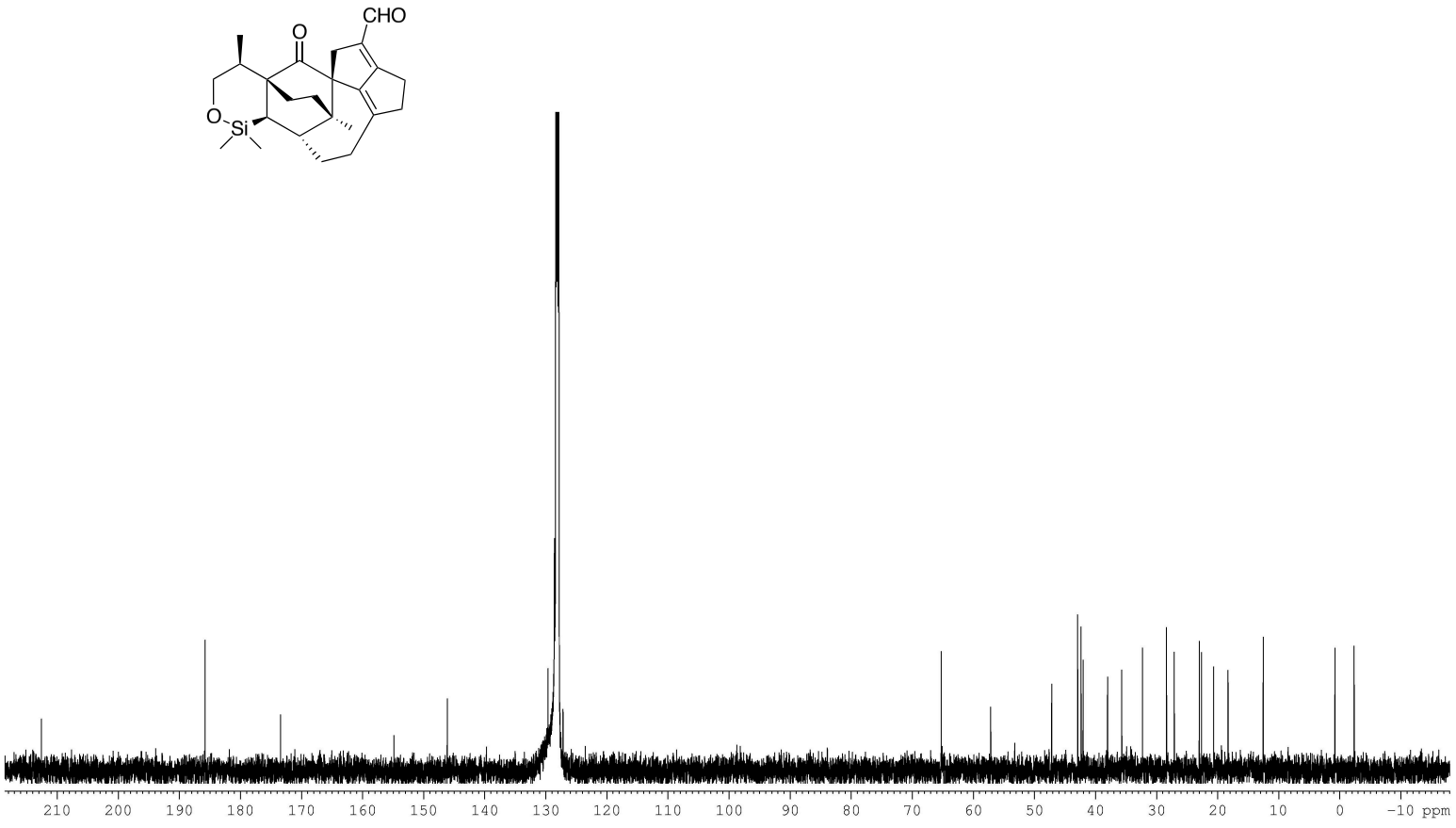



**Figure A2-62:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.28** in $C_6D_6$

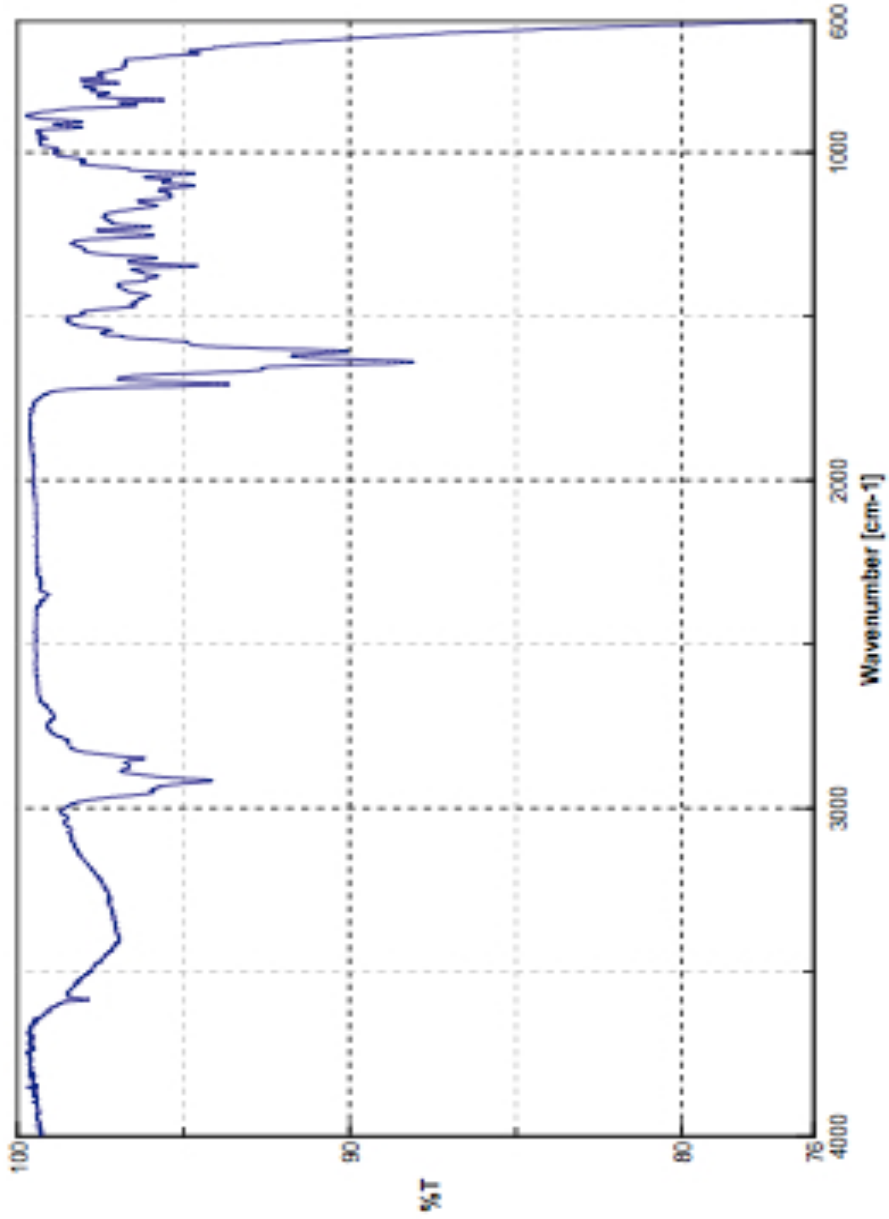



**Figure A2-63:** The Infrared Spectrum of Compound (+)-**3.28**

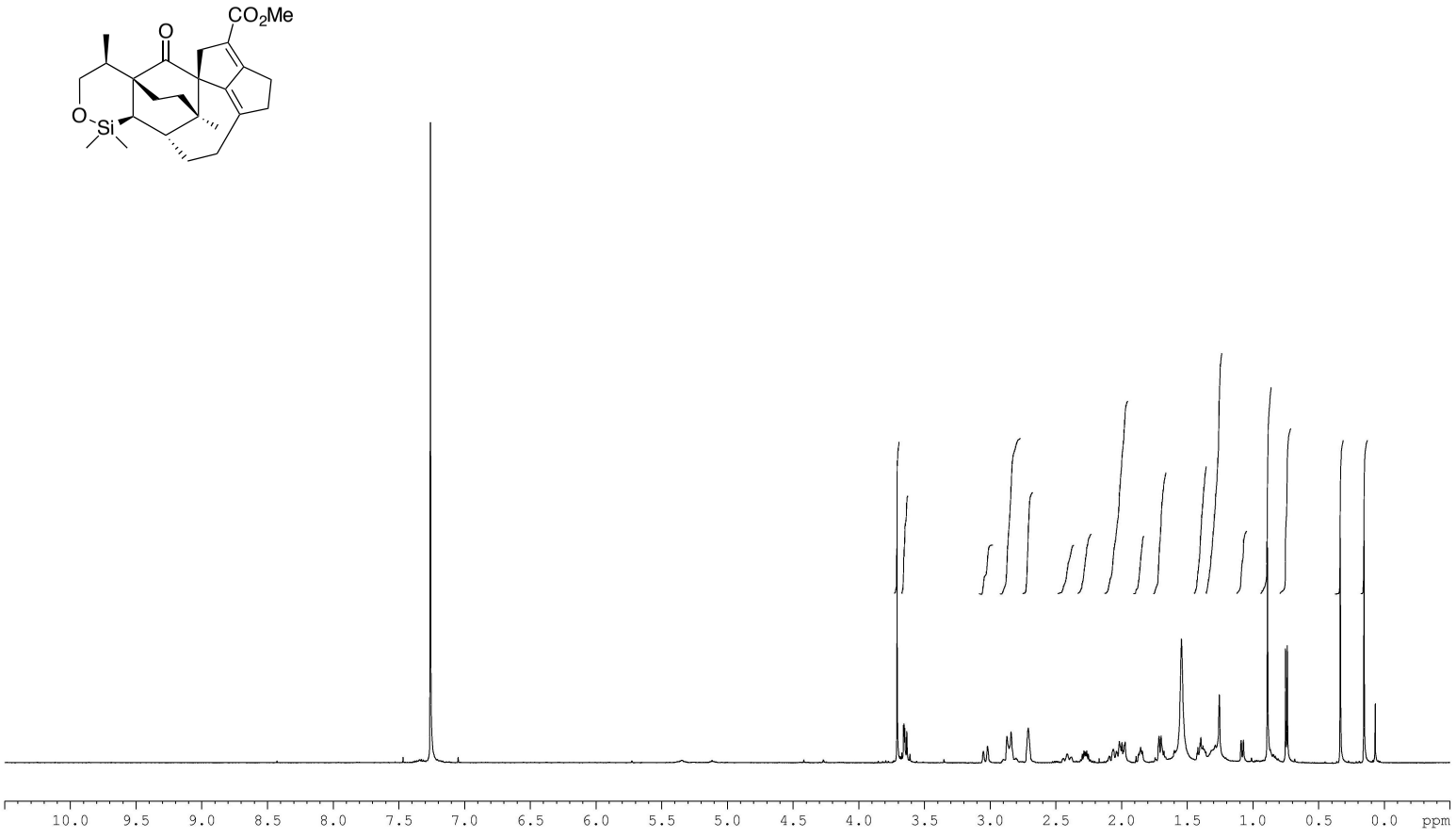



**Figure A2-64:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.29** in $CDCl_3$

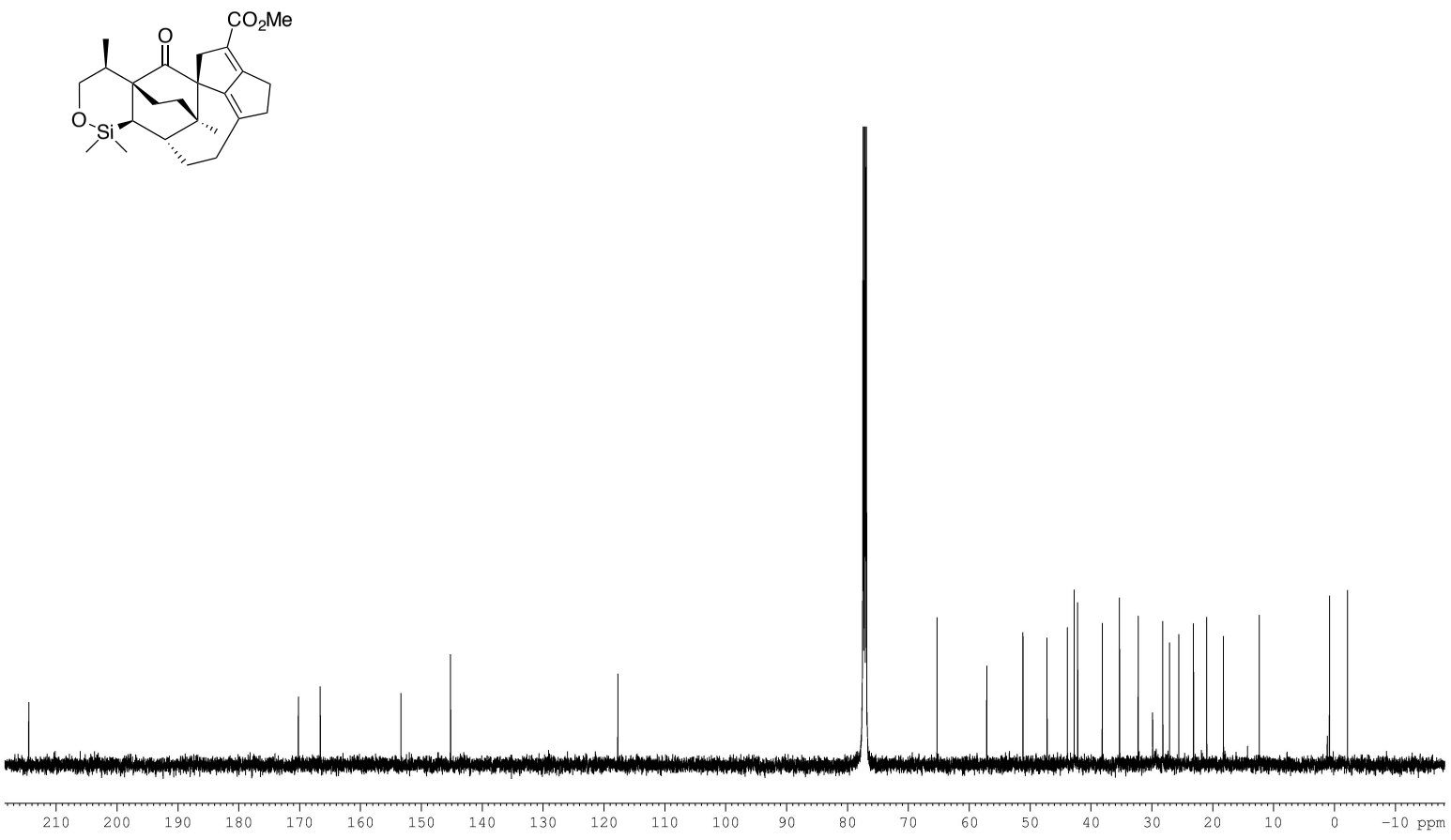



**Figure A2-65:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.29** in $CDCl_3$

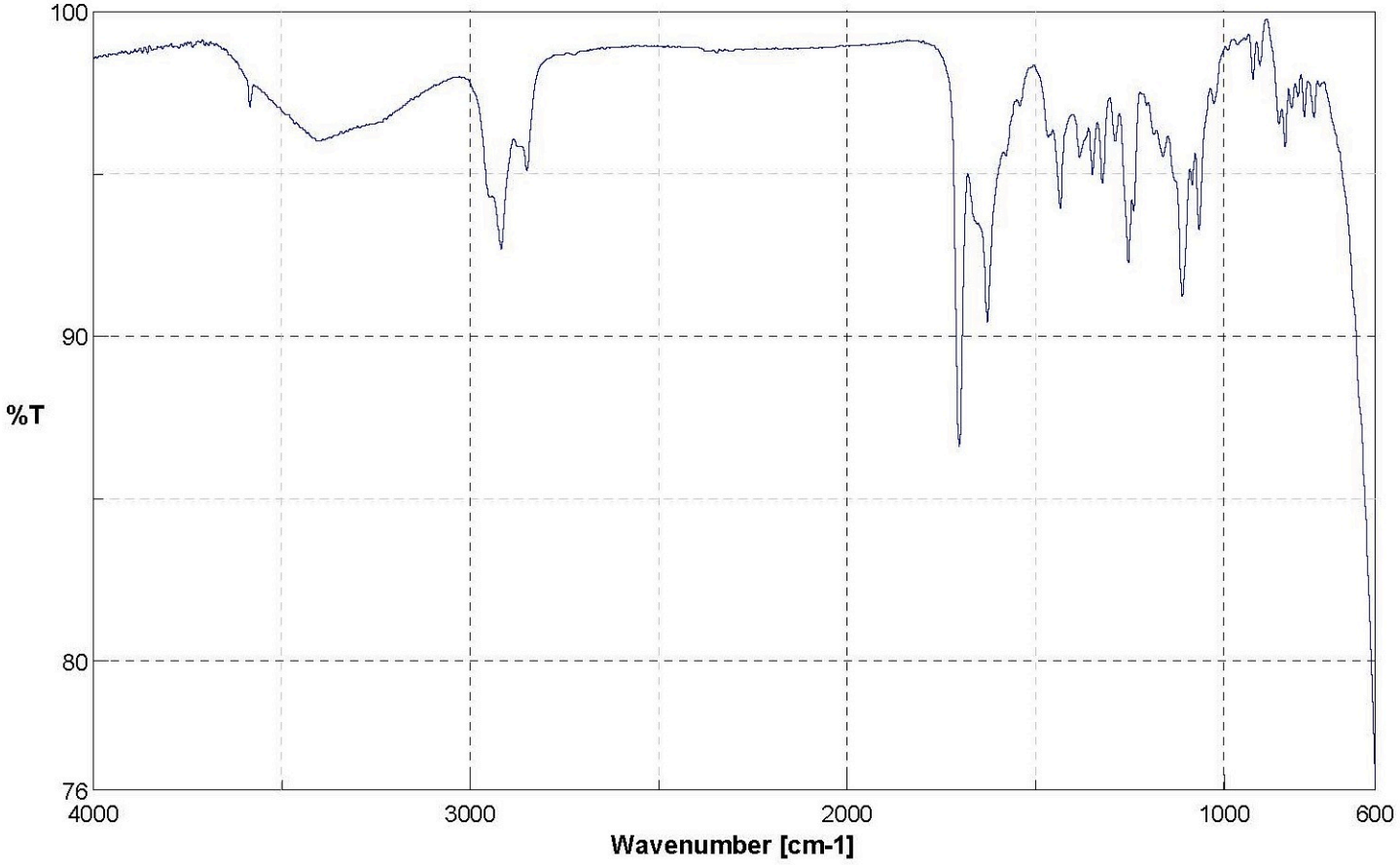



**Figure A2-66:** The Infrared Spectrum of Compound (+)-**3.29**

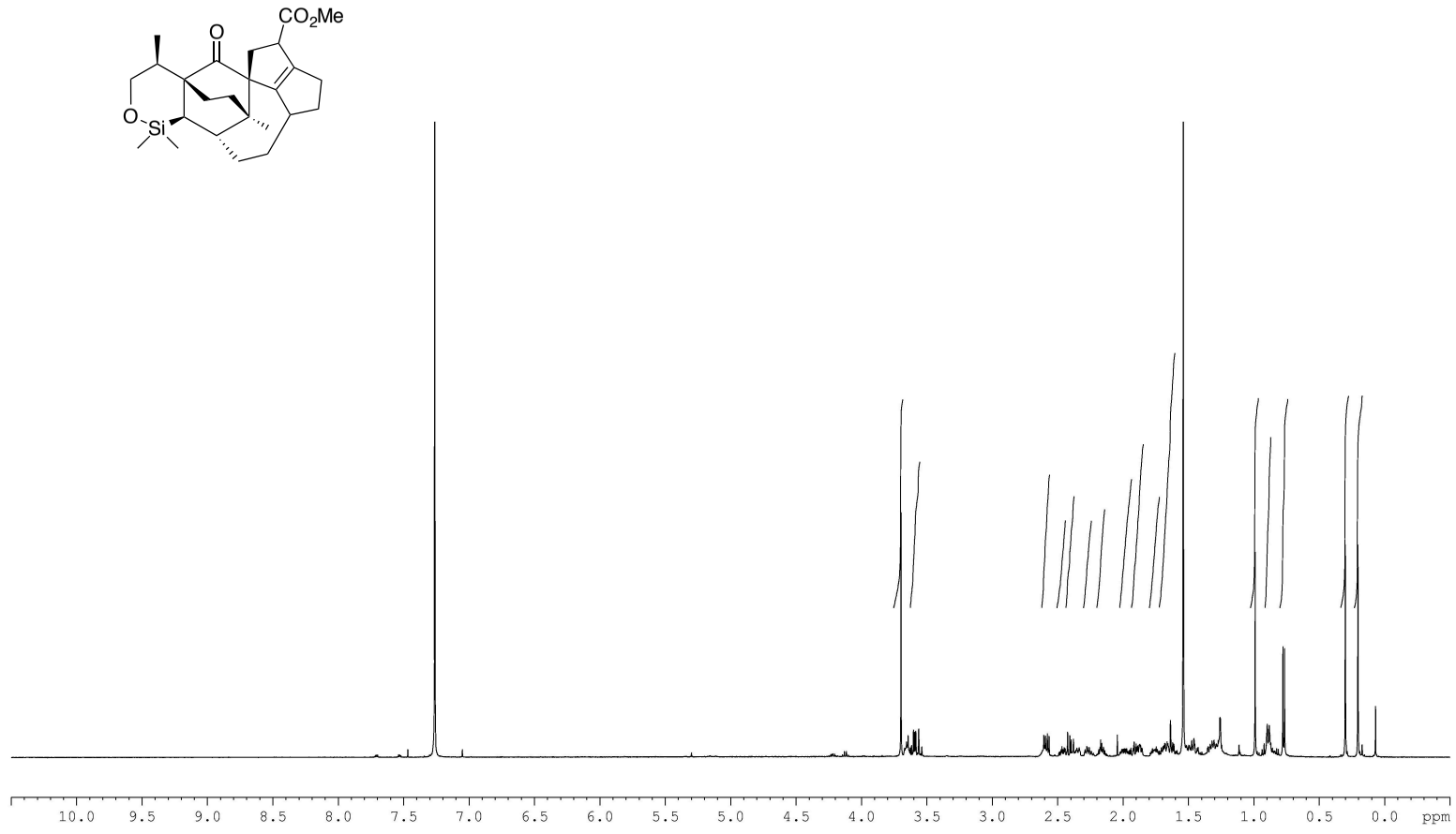



**Figure A2-67:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.31** in $CDCl_3$

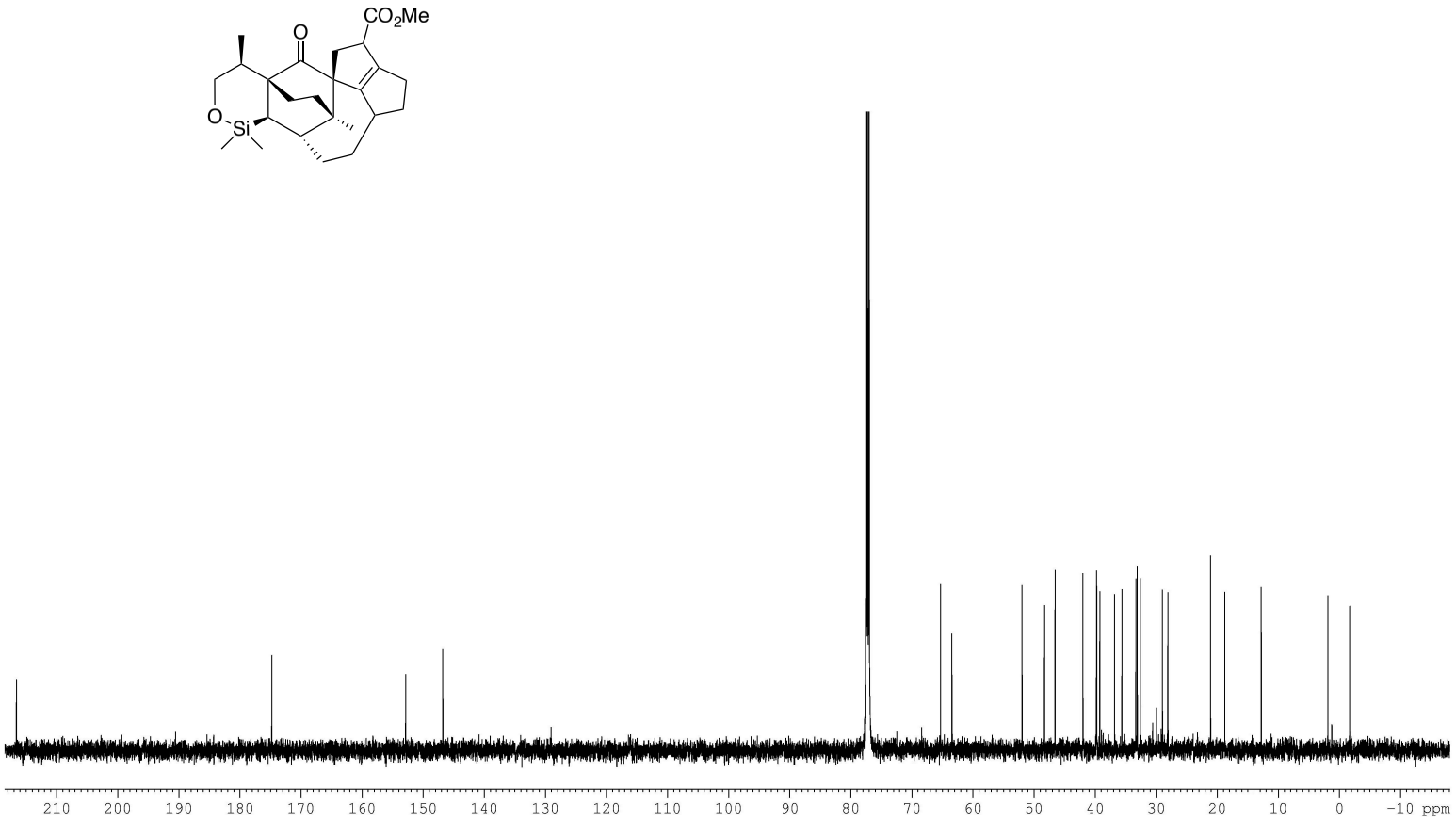



**Figure A2-68:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.31** in $CDCl_3$

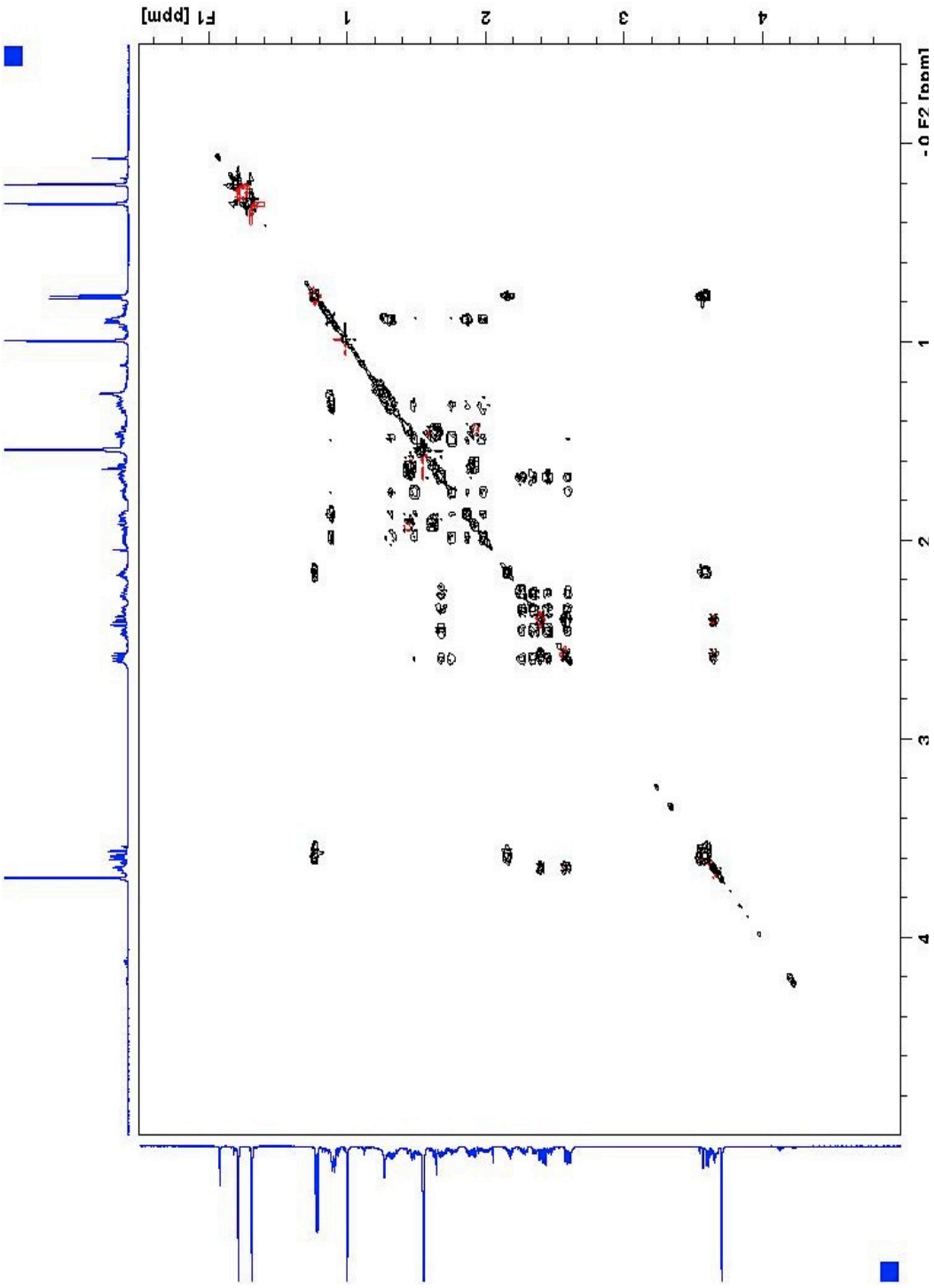



**Figure A2-69:** The HSQC Spectrum of Compound (+)-**3.31** in $CDCl_3$

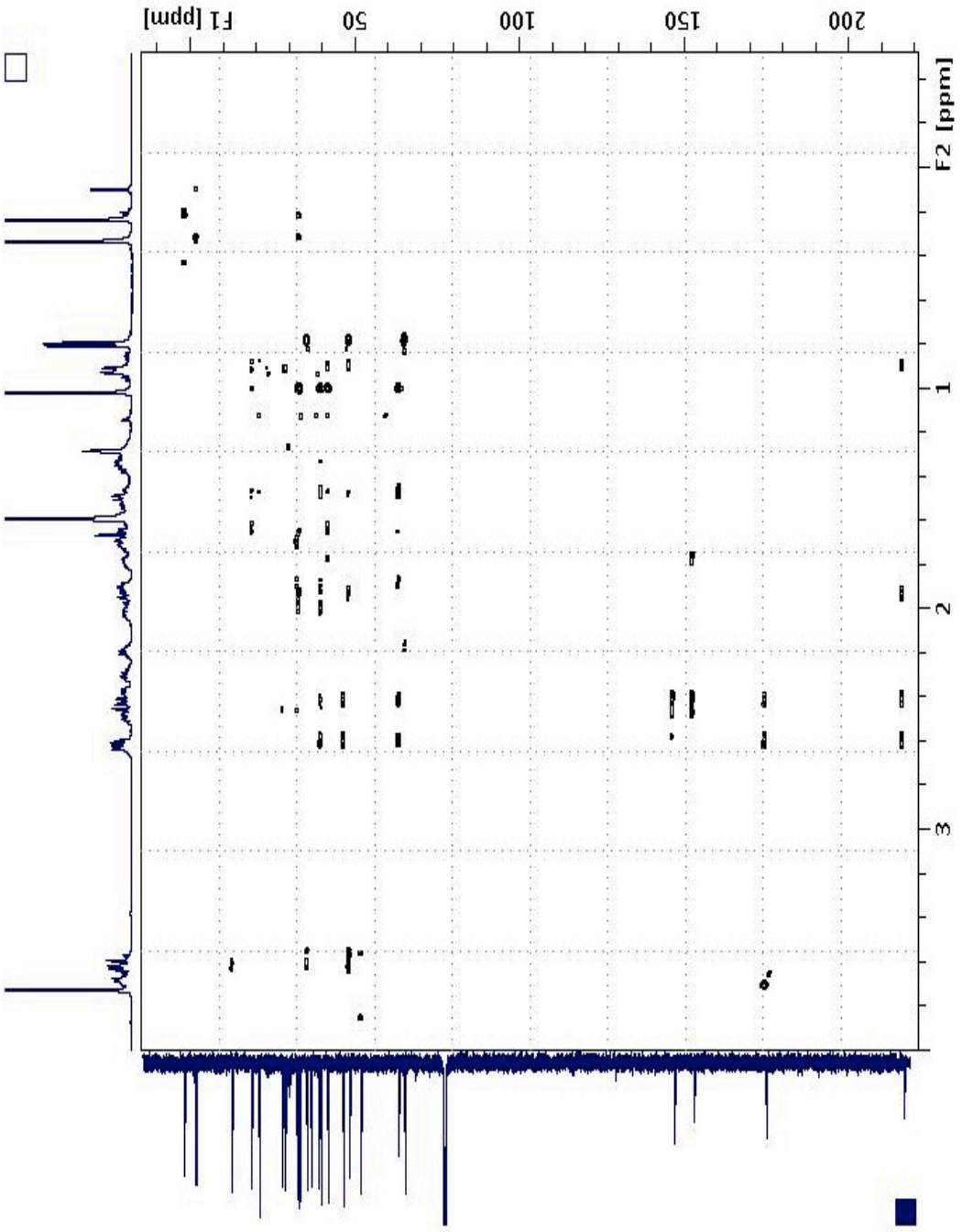



**Figure A2-70:** The HMBC Spectrum of Compound (+)-**3.31** in $CDCl_3$

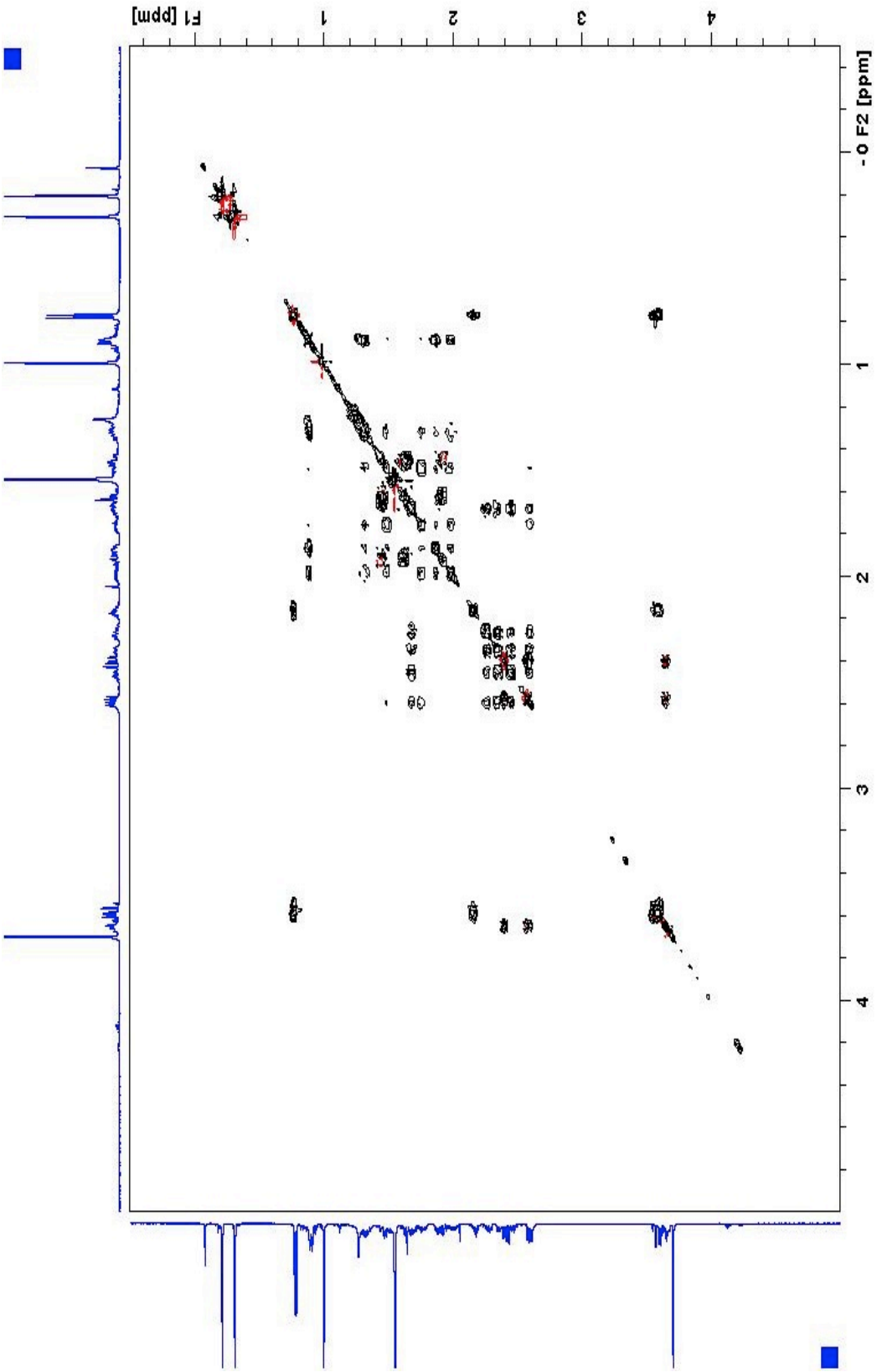



**Figure A2-71:** The TOCSY Spectrum of Compound (+)-**3.31** in $CDCl_3$

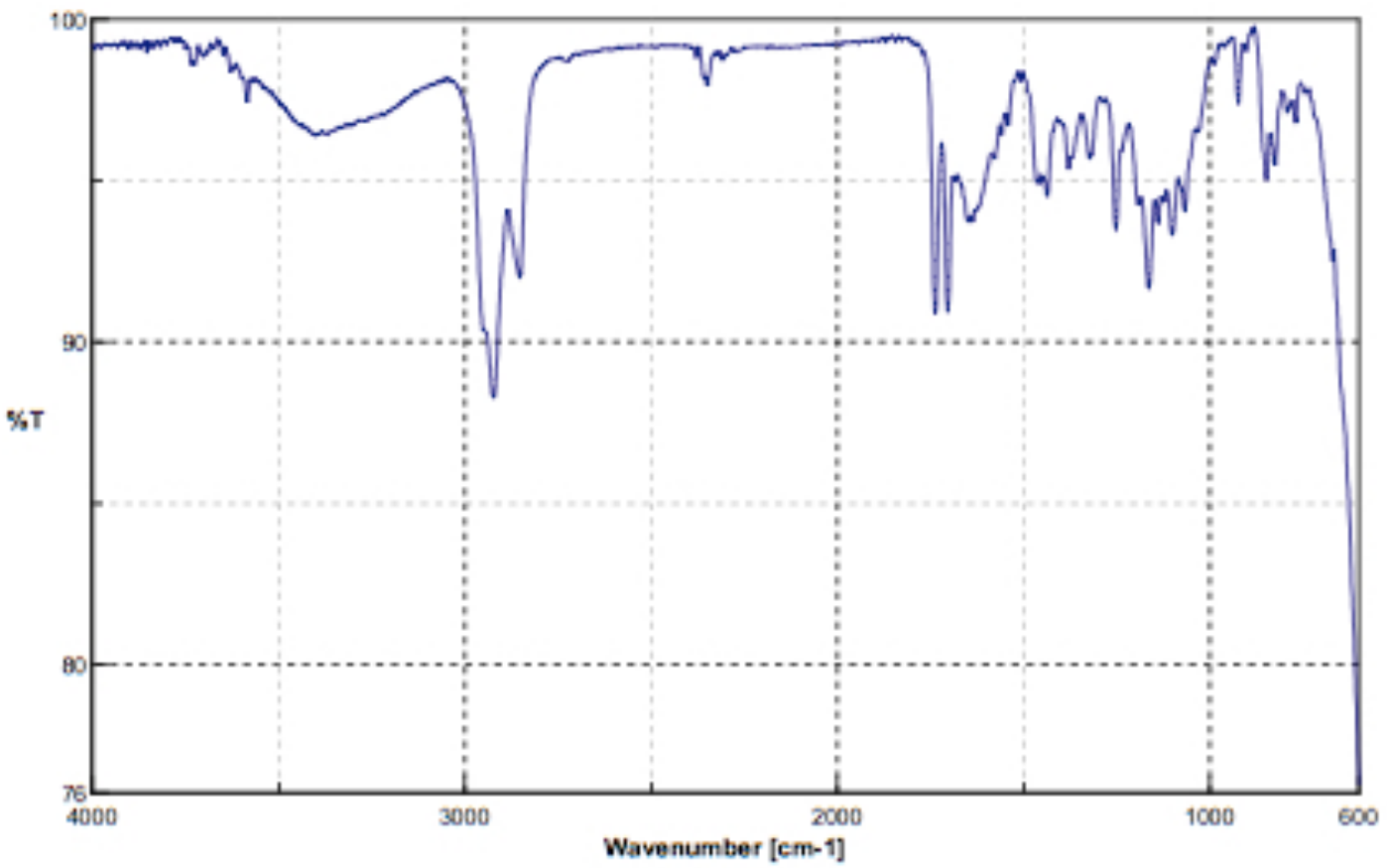



**Figure A2-72:** The Infrared Spectrum of Compound (+)-**3.31**

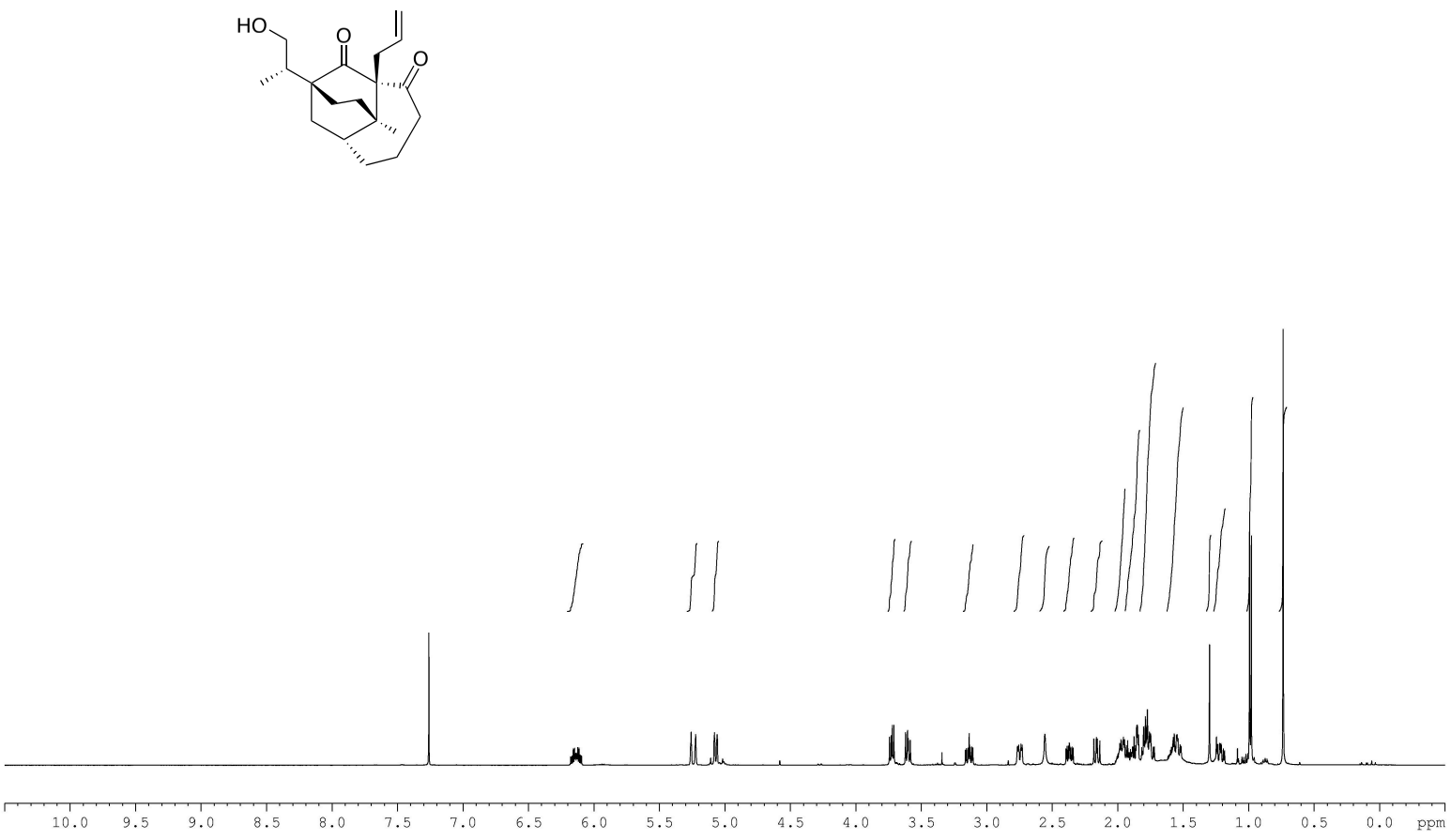



**Figure A2-73:** The 500 MHz $^{1}$H NMR Spectrum of Compound **3.34** in $CDCl_3$

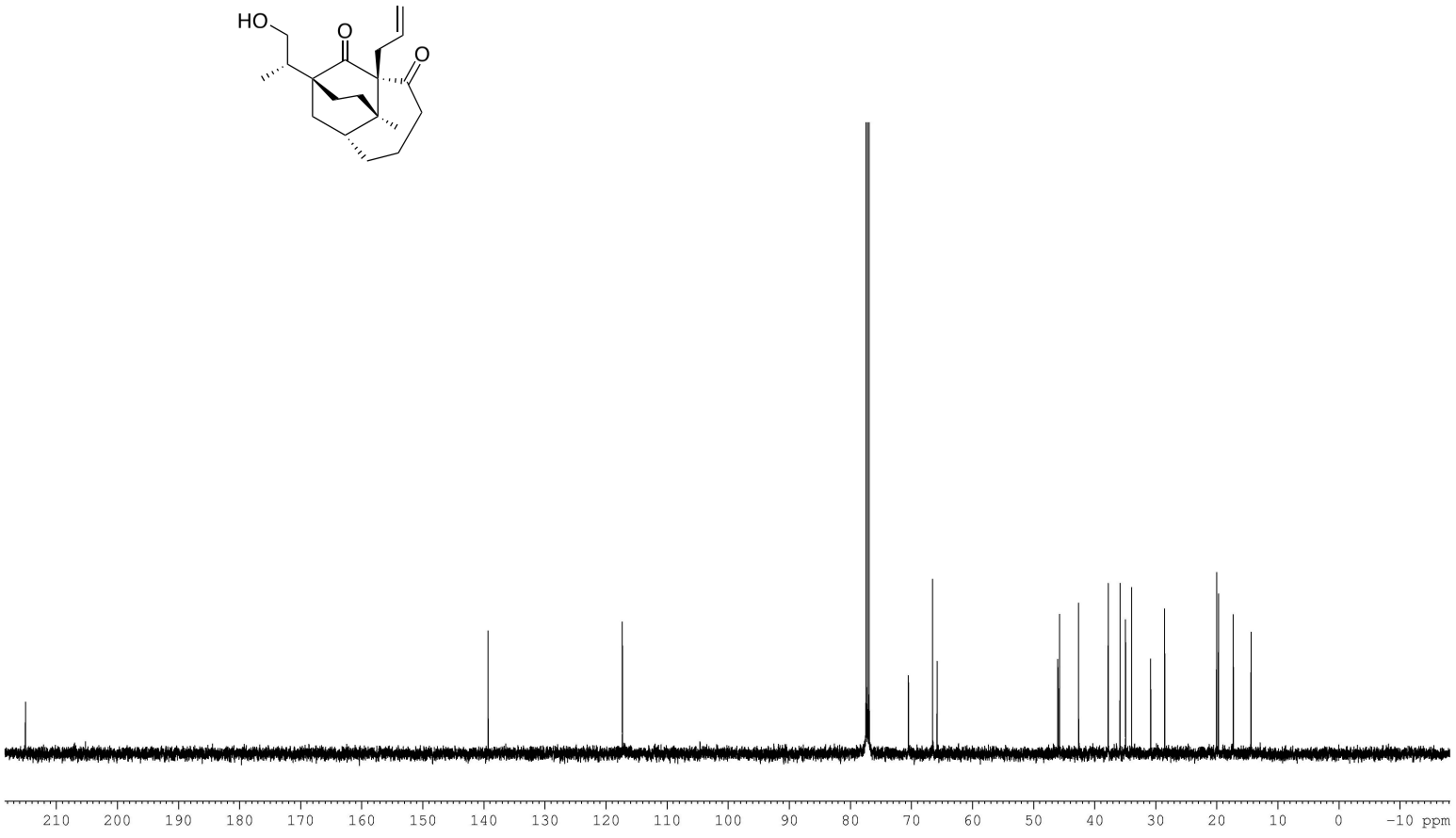



**Figure A2-74:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.36** in $CDCl_3$

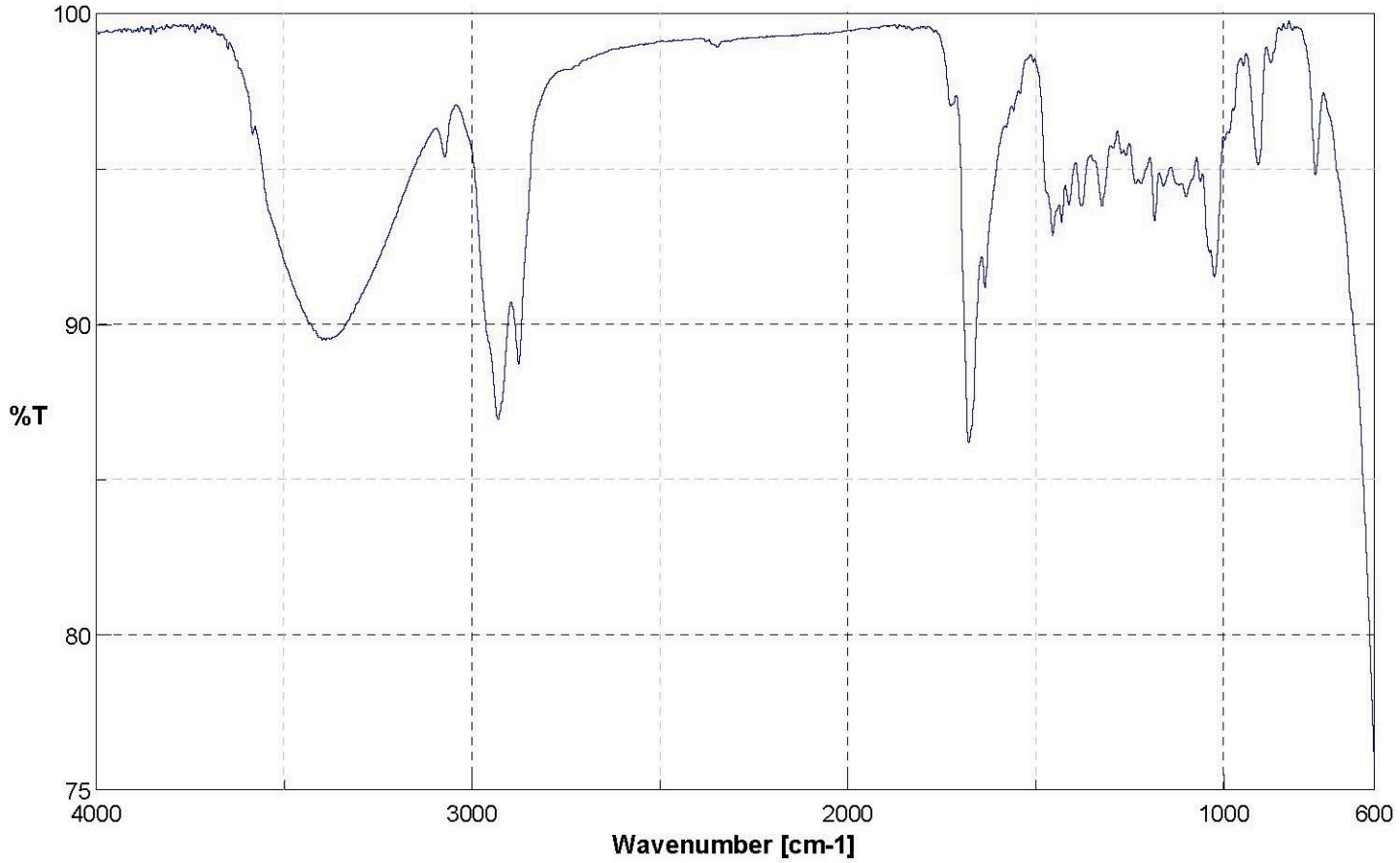



**Figure A2-75:** The Infrared Spectrum of Compound (+)-**3.36**

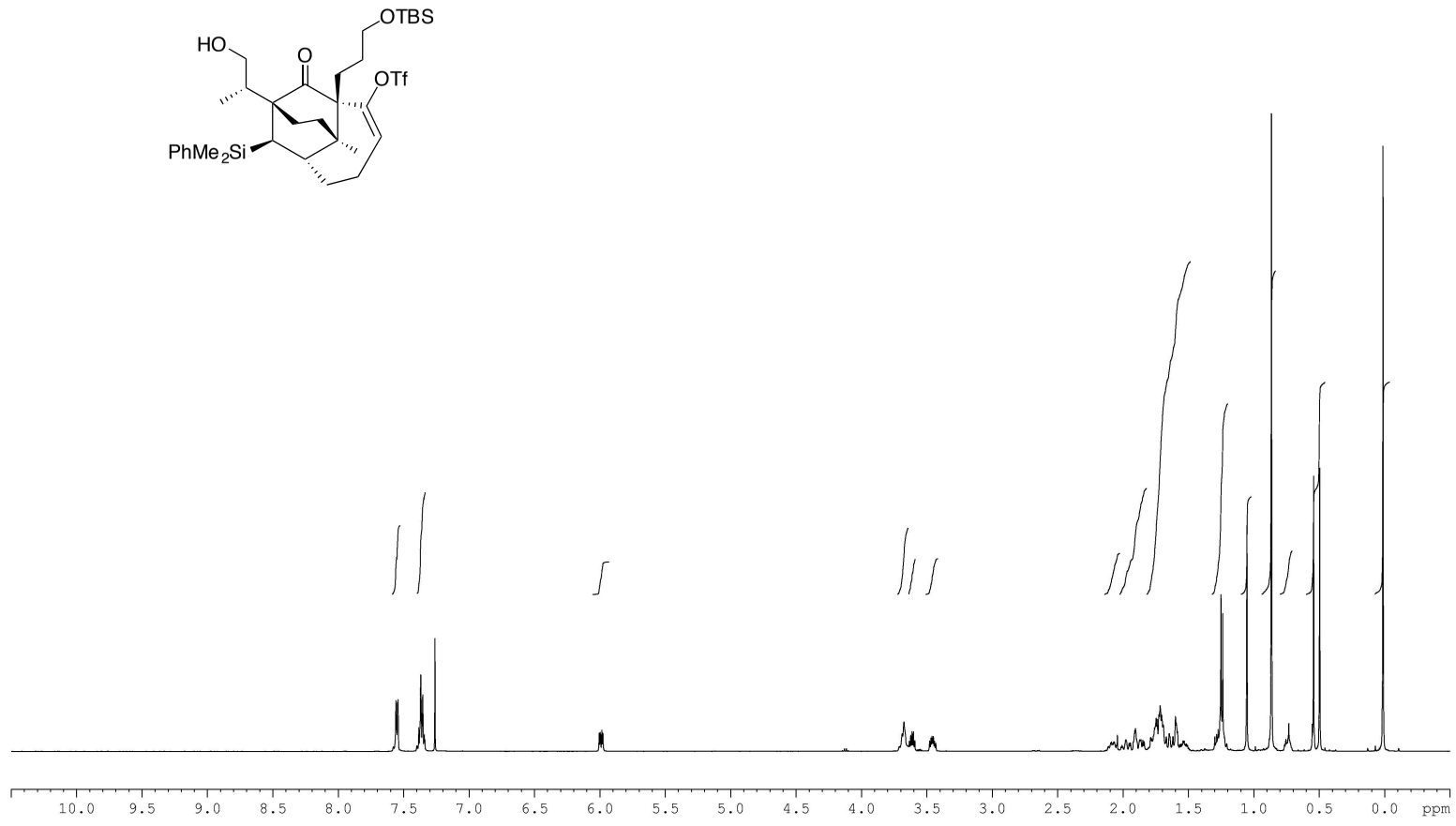



**Figure A2-76:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.43** in $CDCl_3$

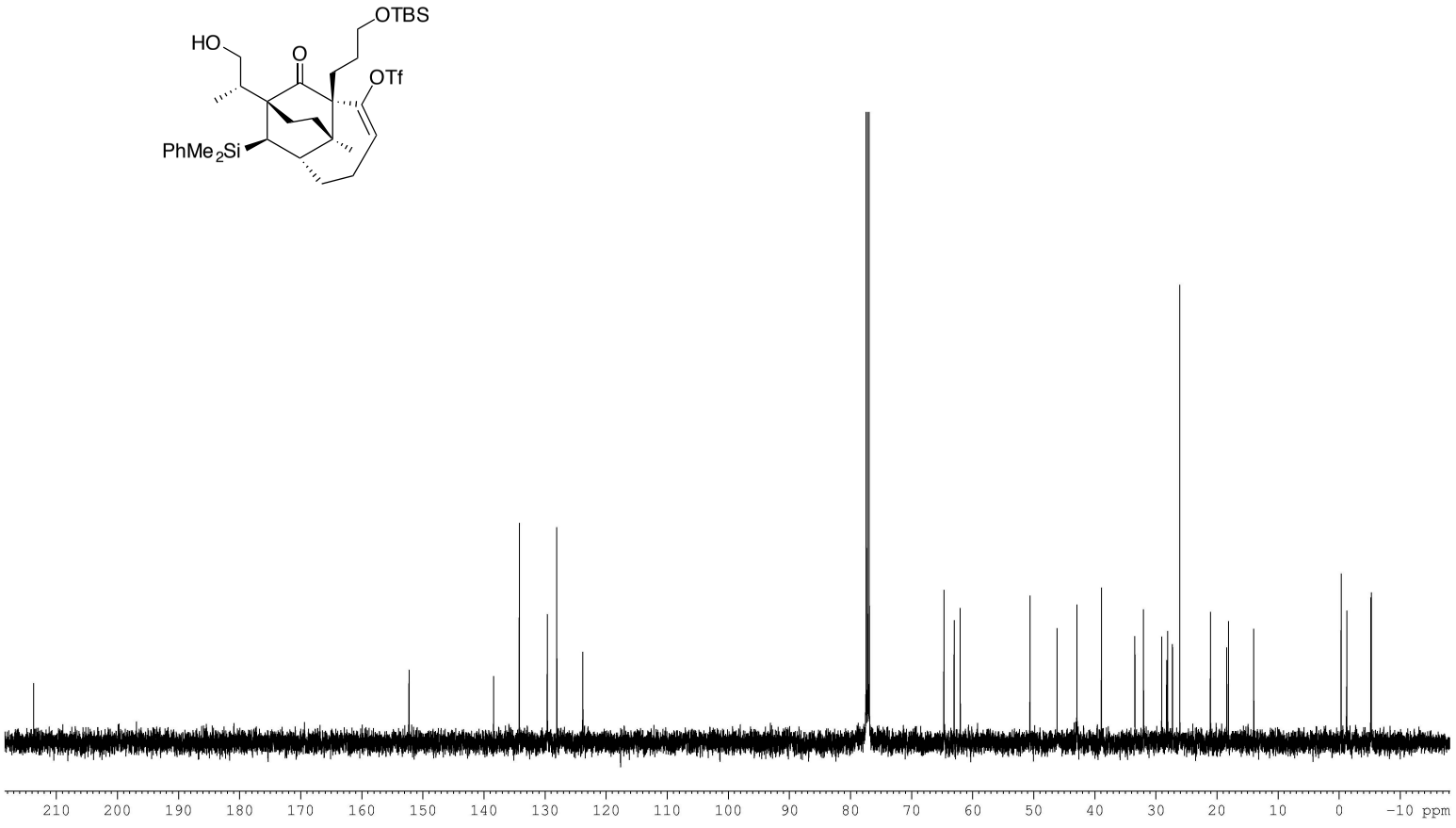



**Figure A2-77:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.43** in $CDCl_3$

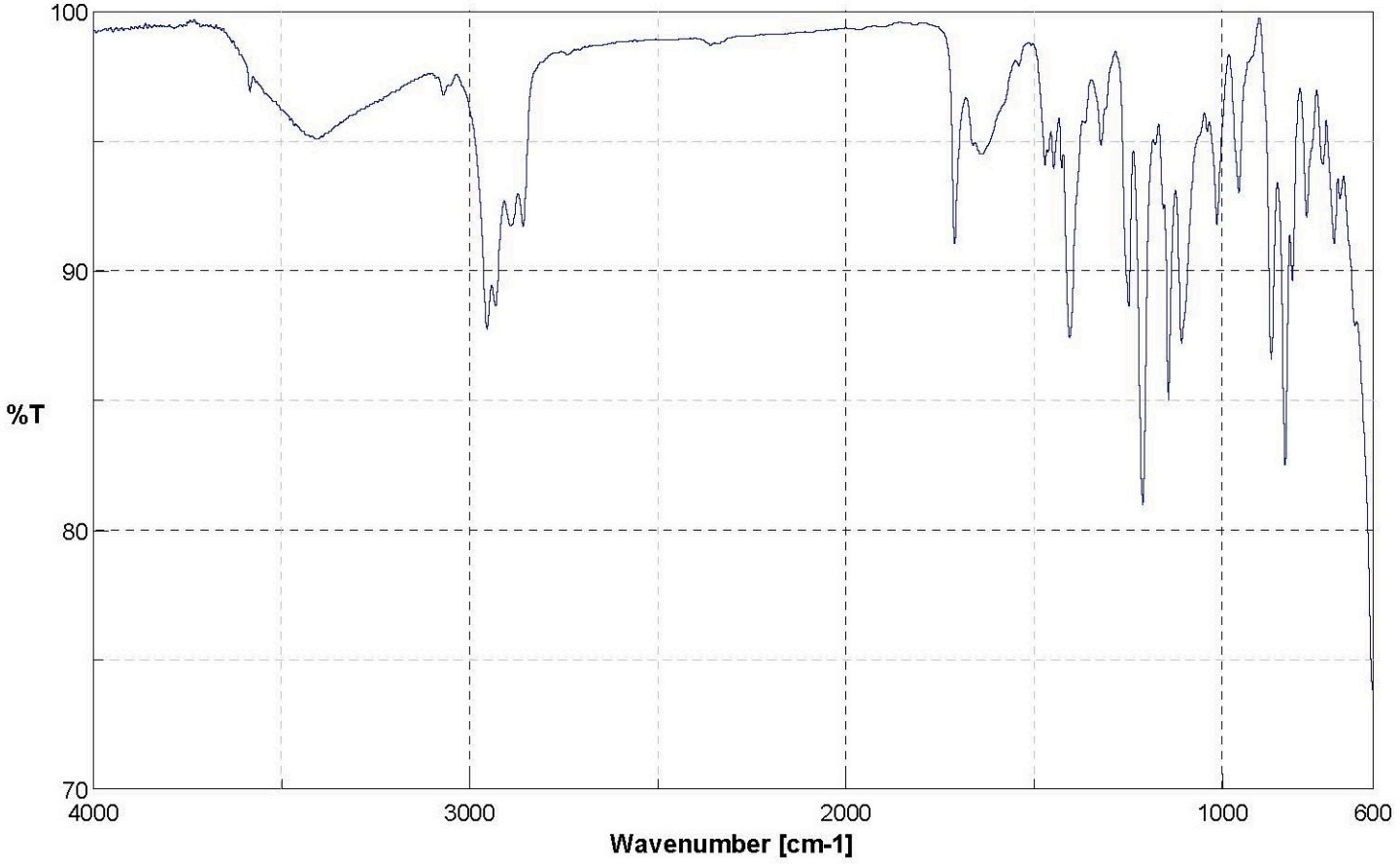



**Figure A2-78:** The Infrared Spectrum of Compound (+)-**3.43**

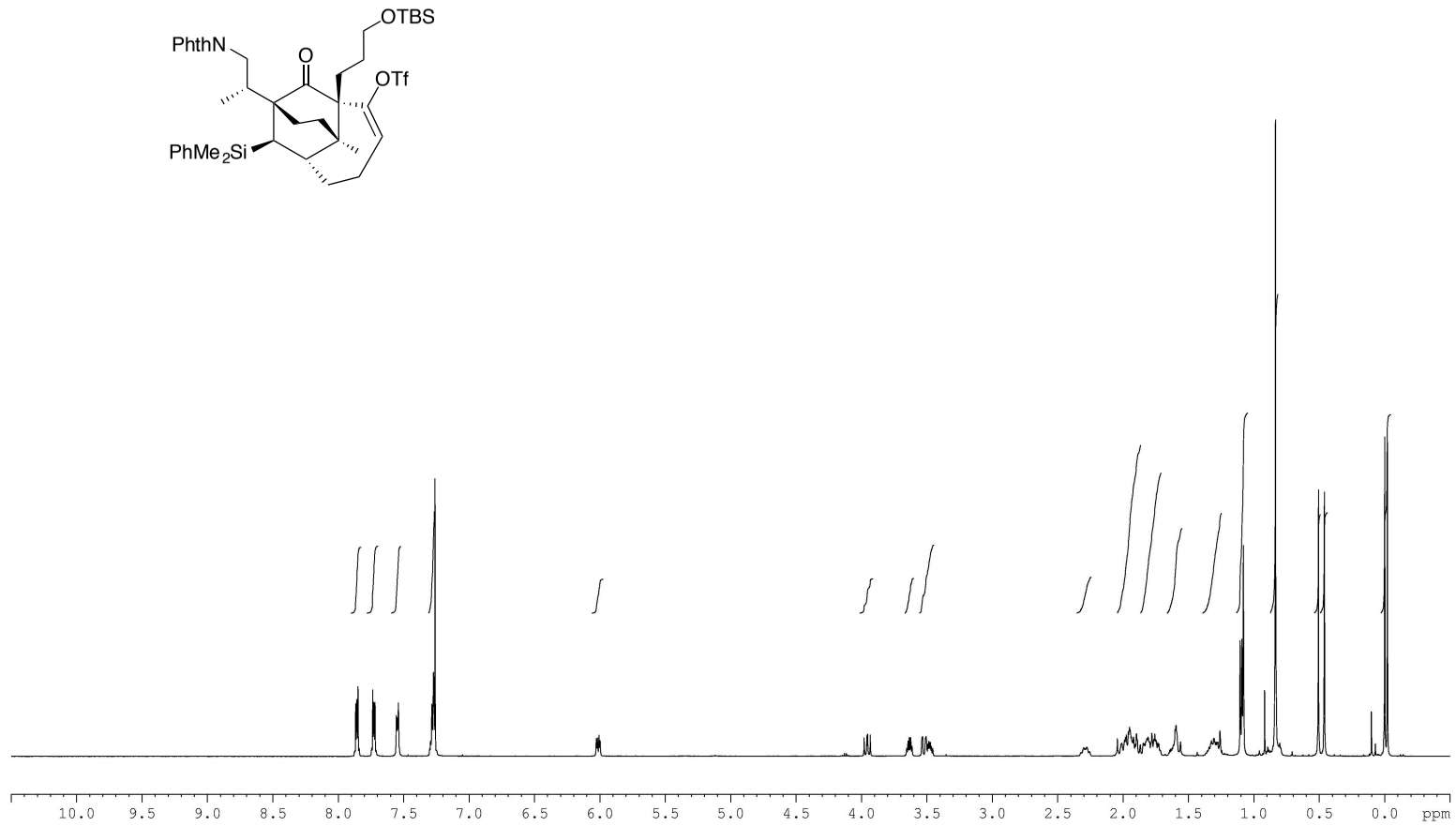



**Figure A2-79:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.44** in $CDCl_3$

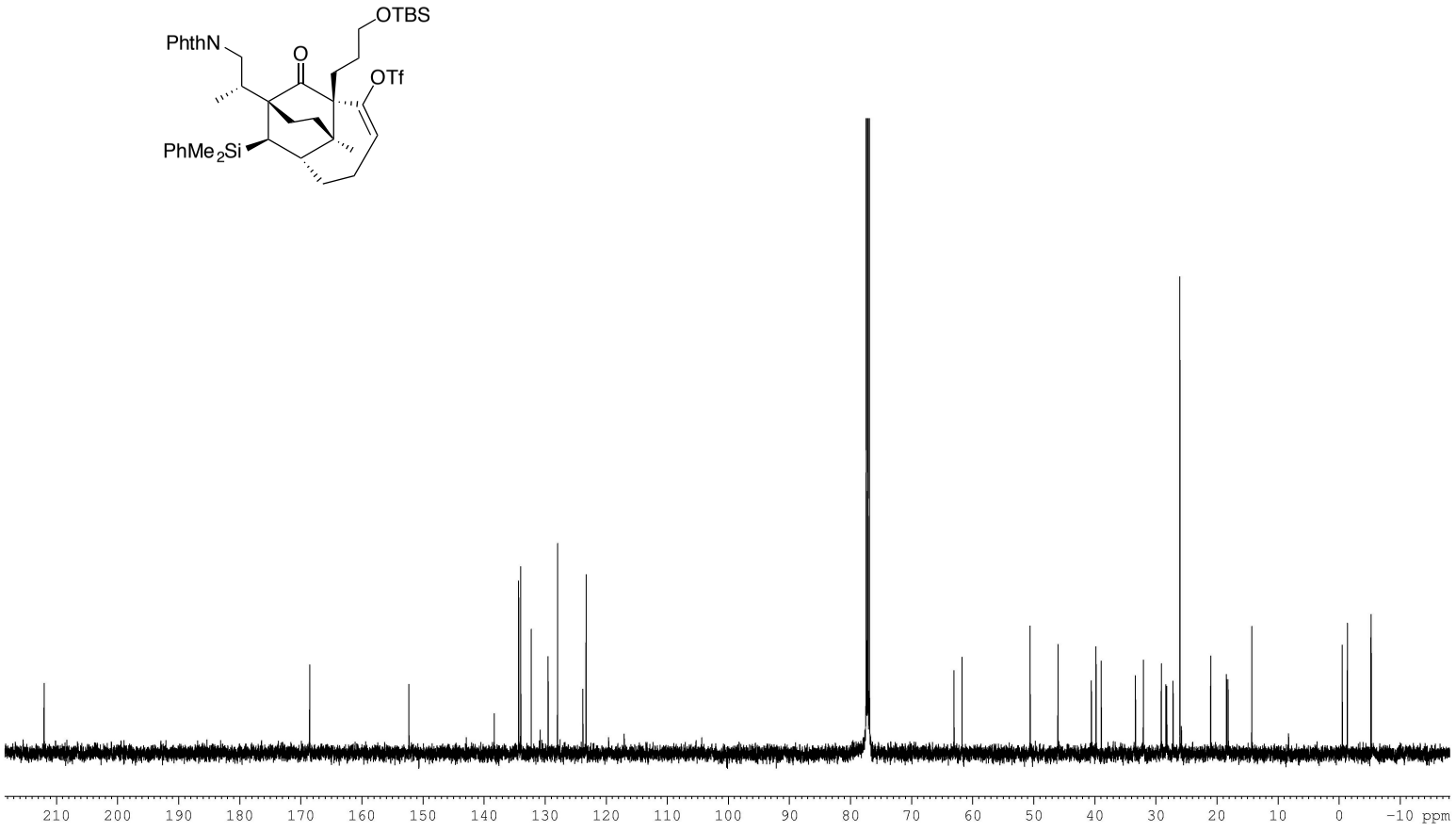



**Figure A2-80:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.44** in $CDCl_3$

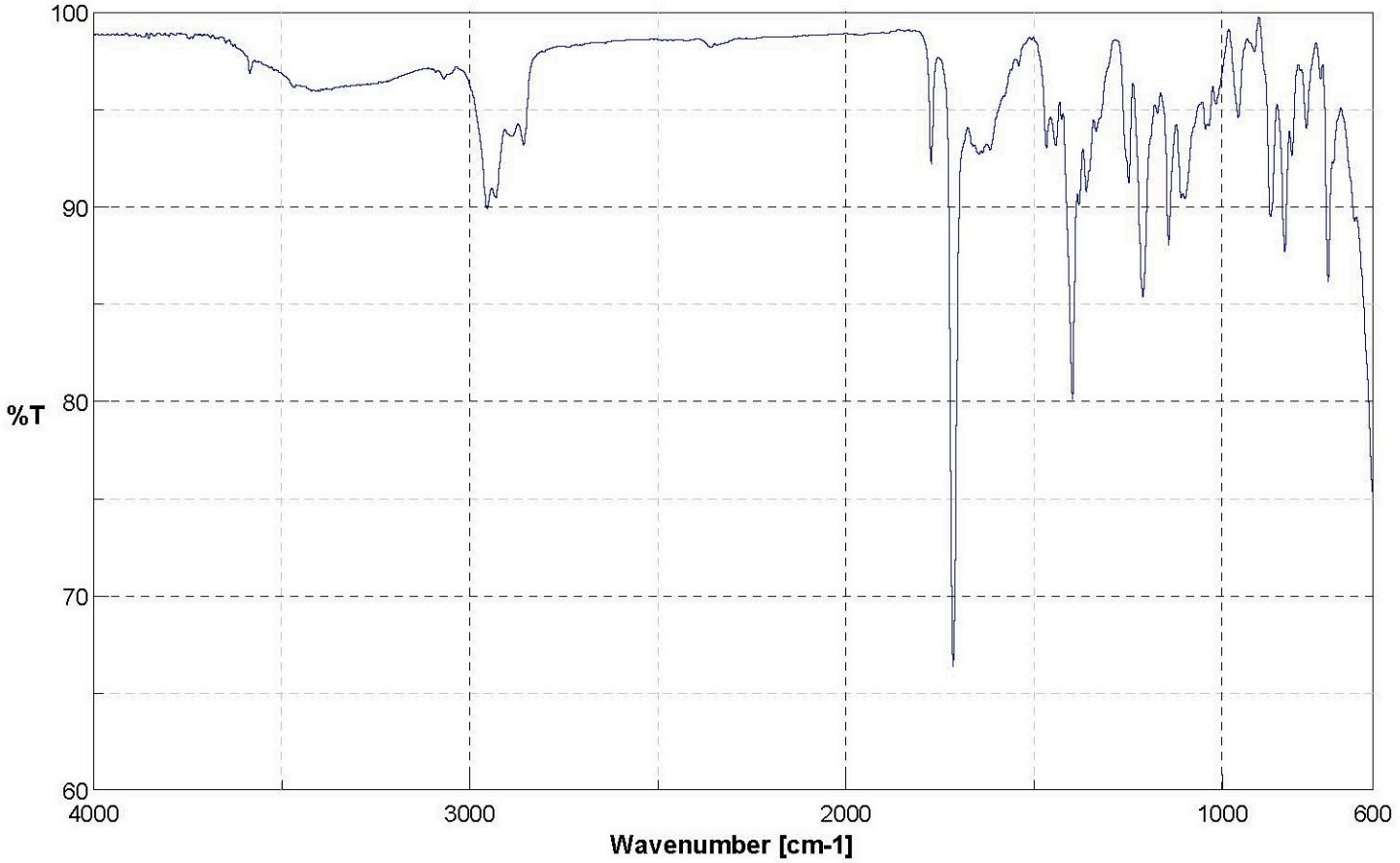



**Figure A2-81:** The Infrared Spectrum of Compound (+)-**3.44**

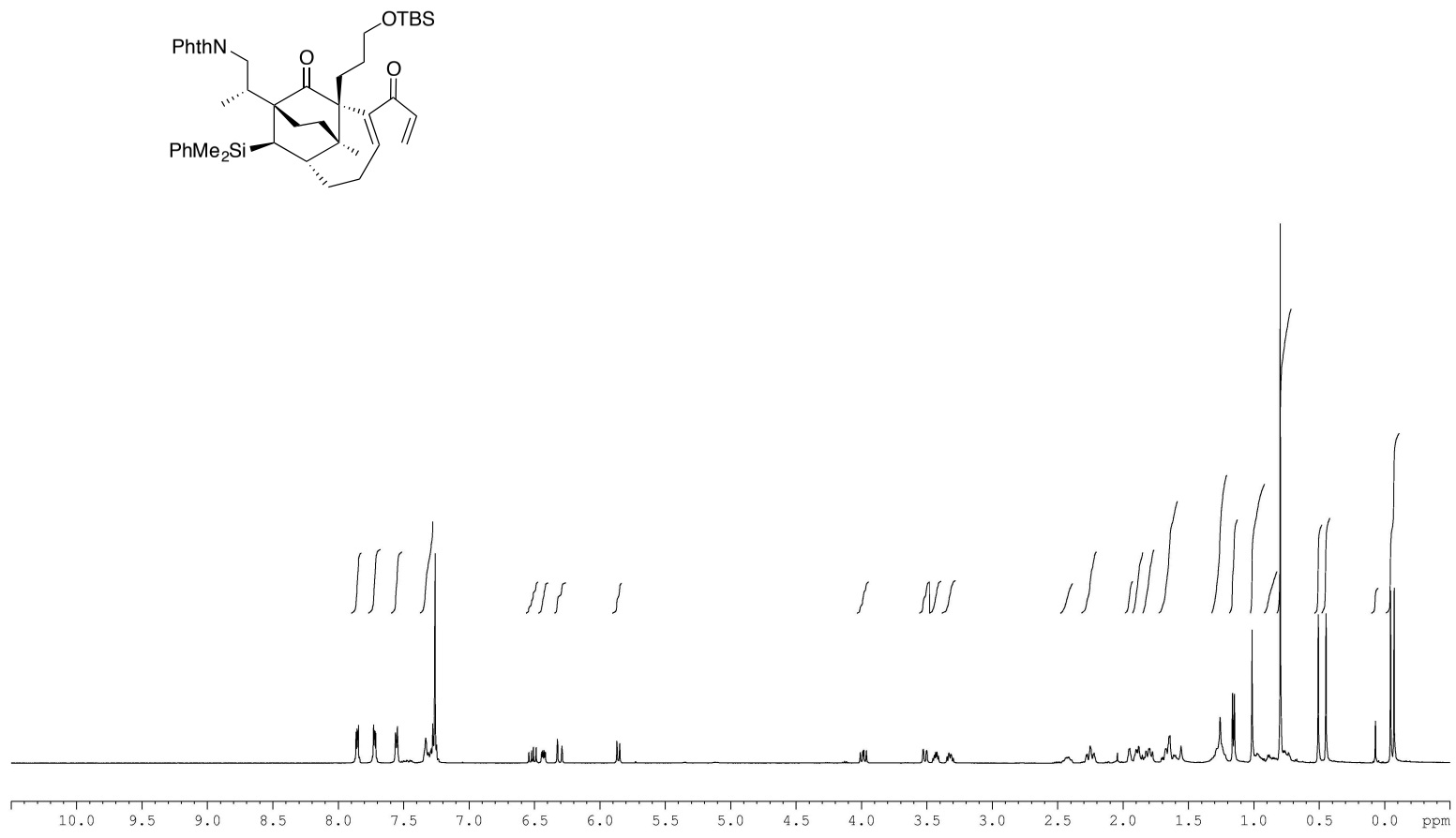



**Figure A2-82:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.45** in $CDCl_3$

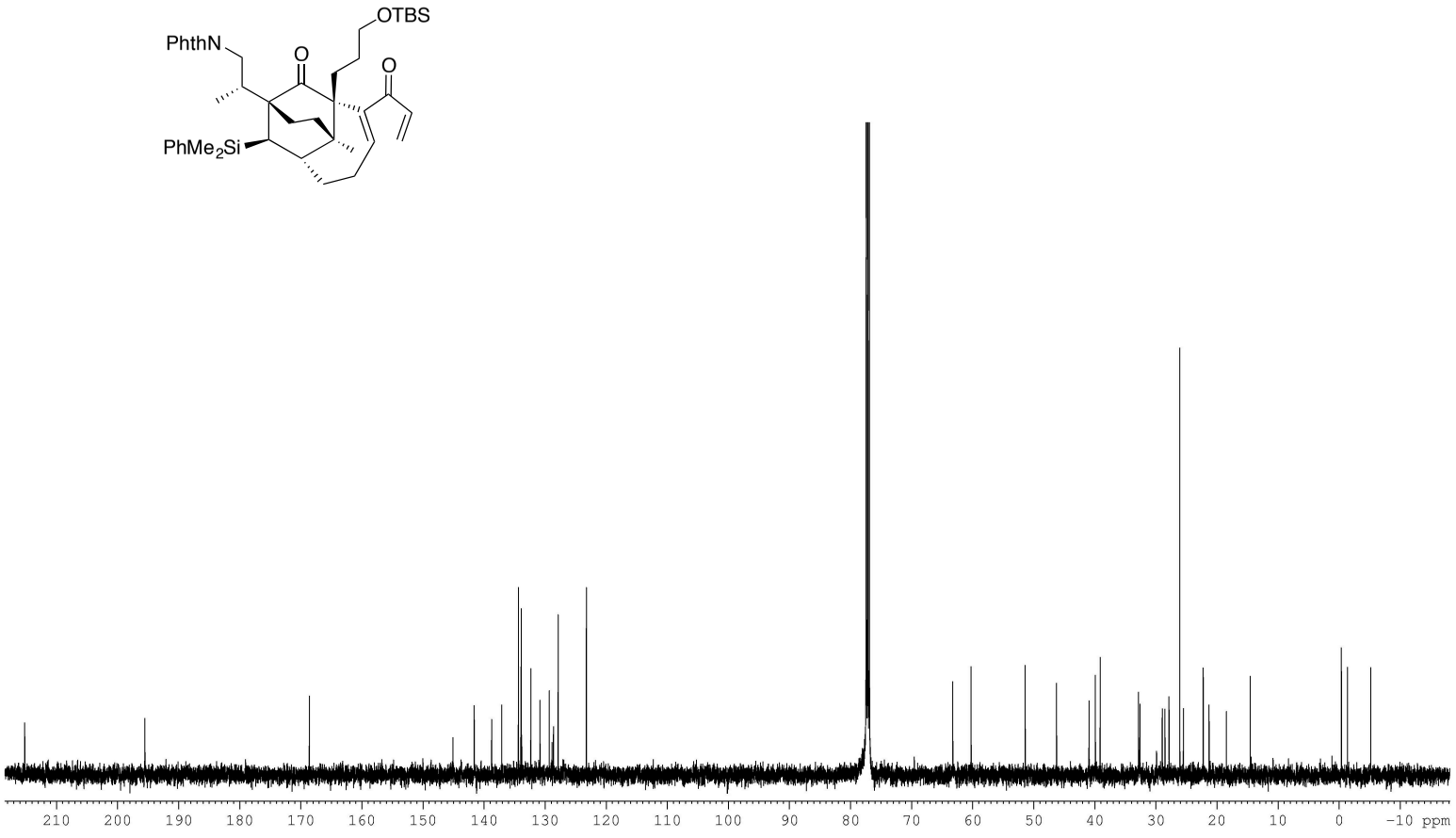



**Figure A2-83:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.45** in $CDCl_3$

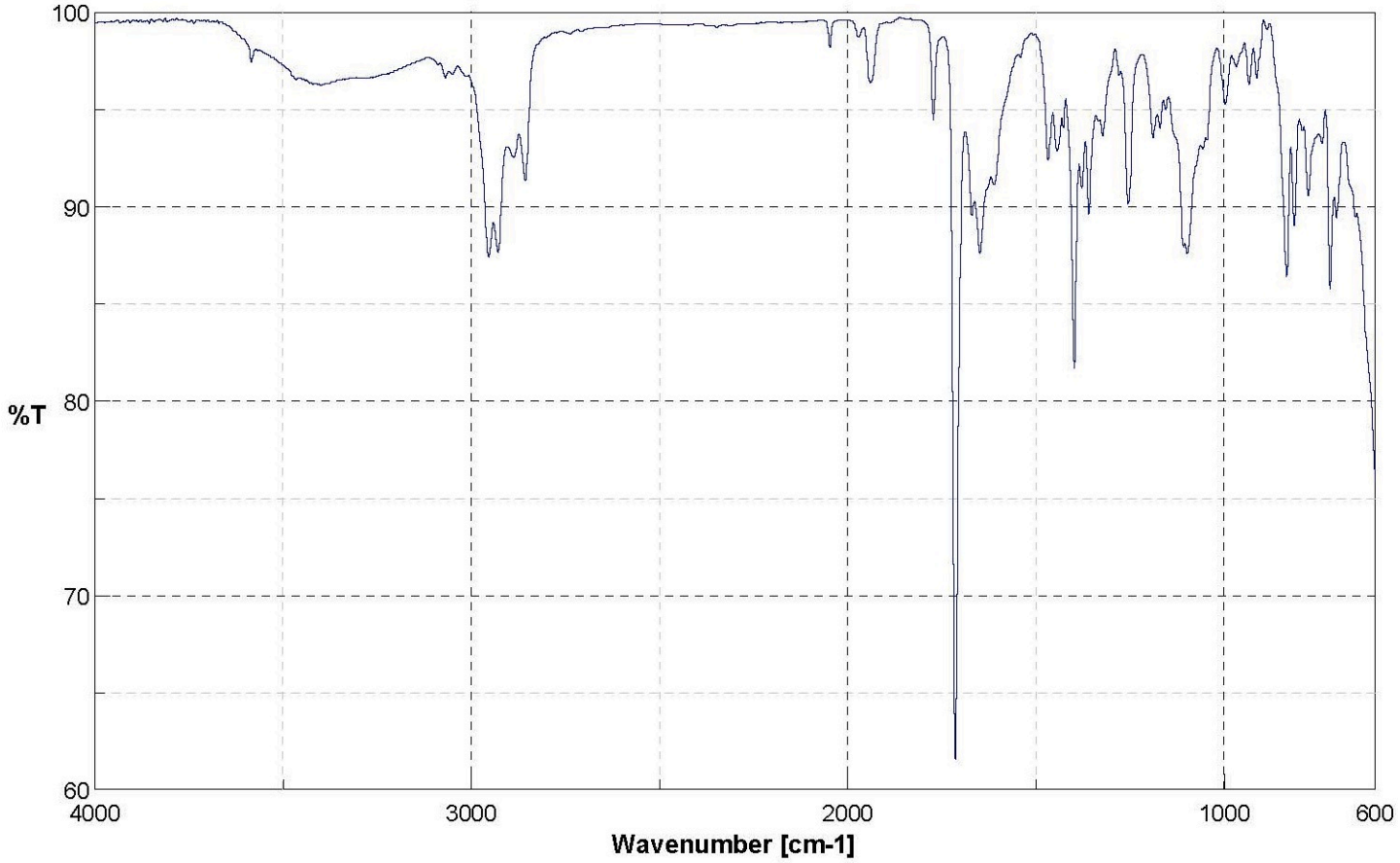



**Figure A2-84:** The Infrared Spectrum of Compound (+)-**3.45**

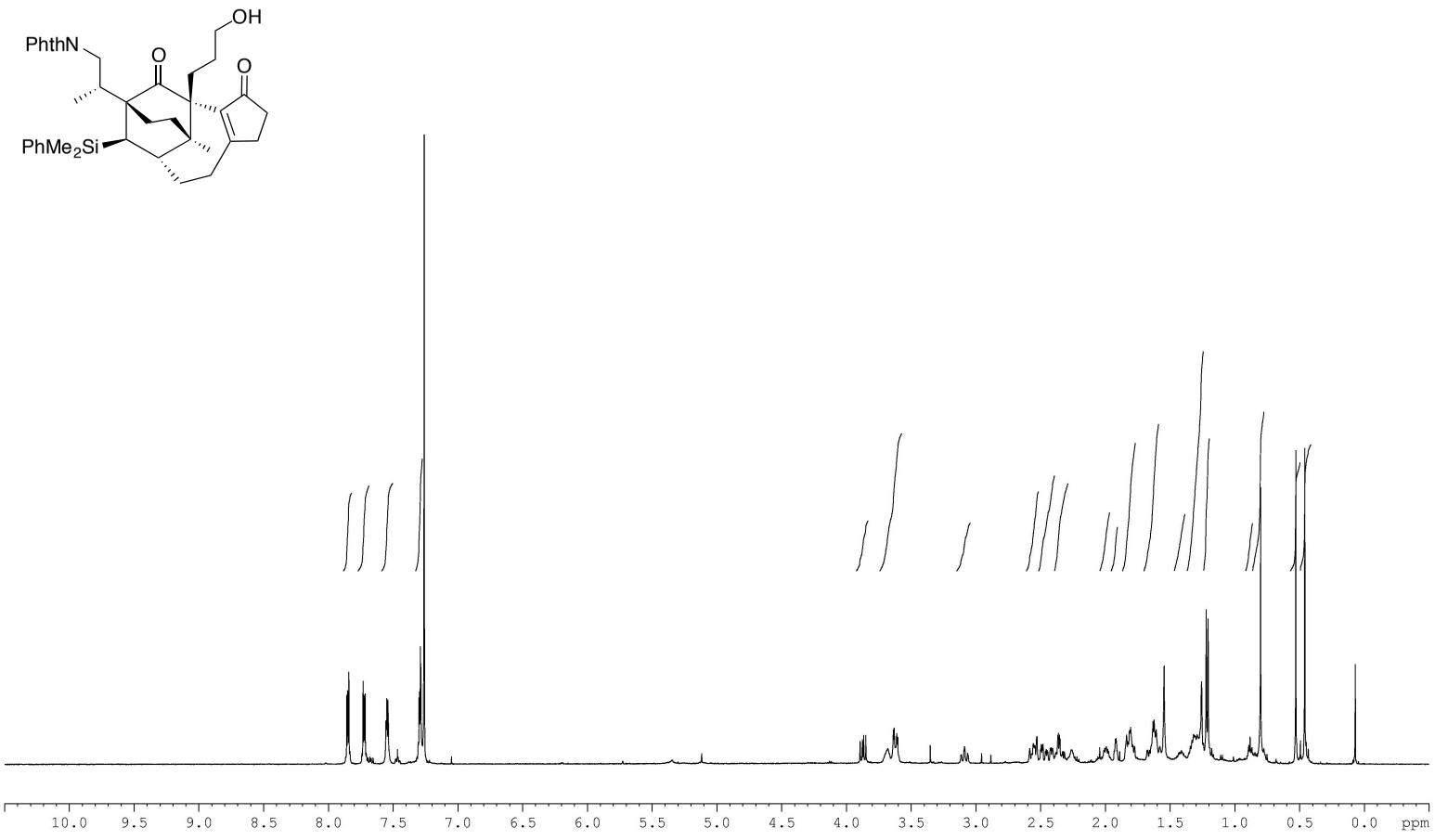



**Figure A2-85:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.46** in $CDCl_3$

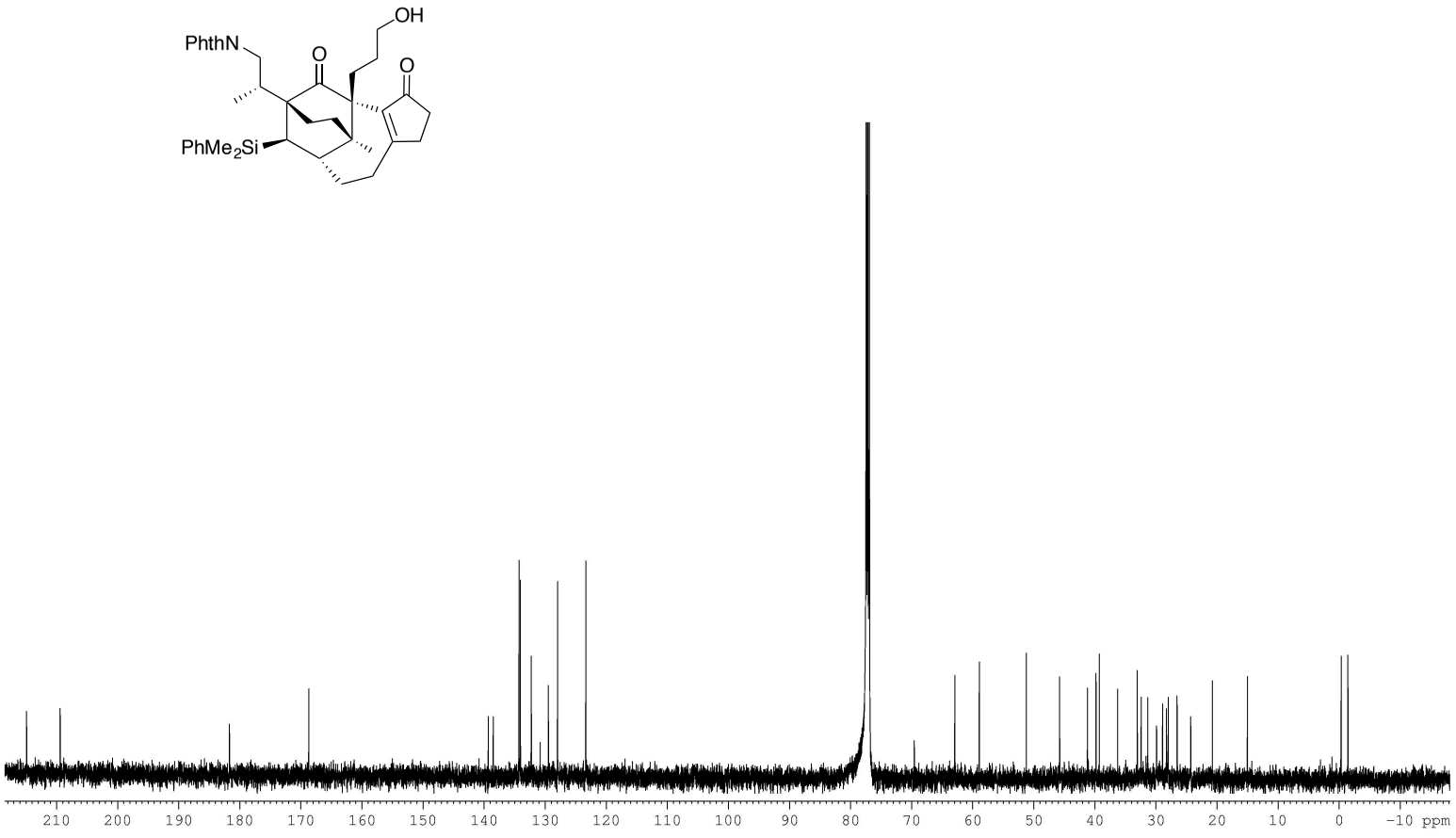



**Figure A2-86:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.46** in $CDCl_3$

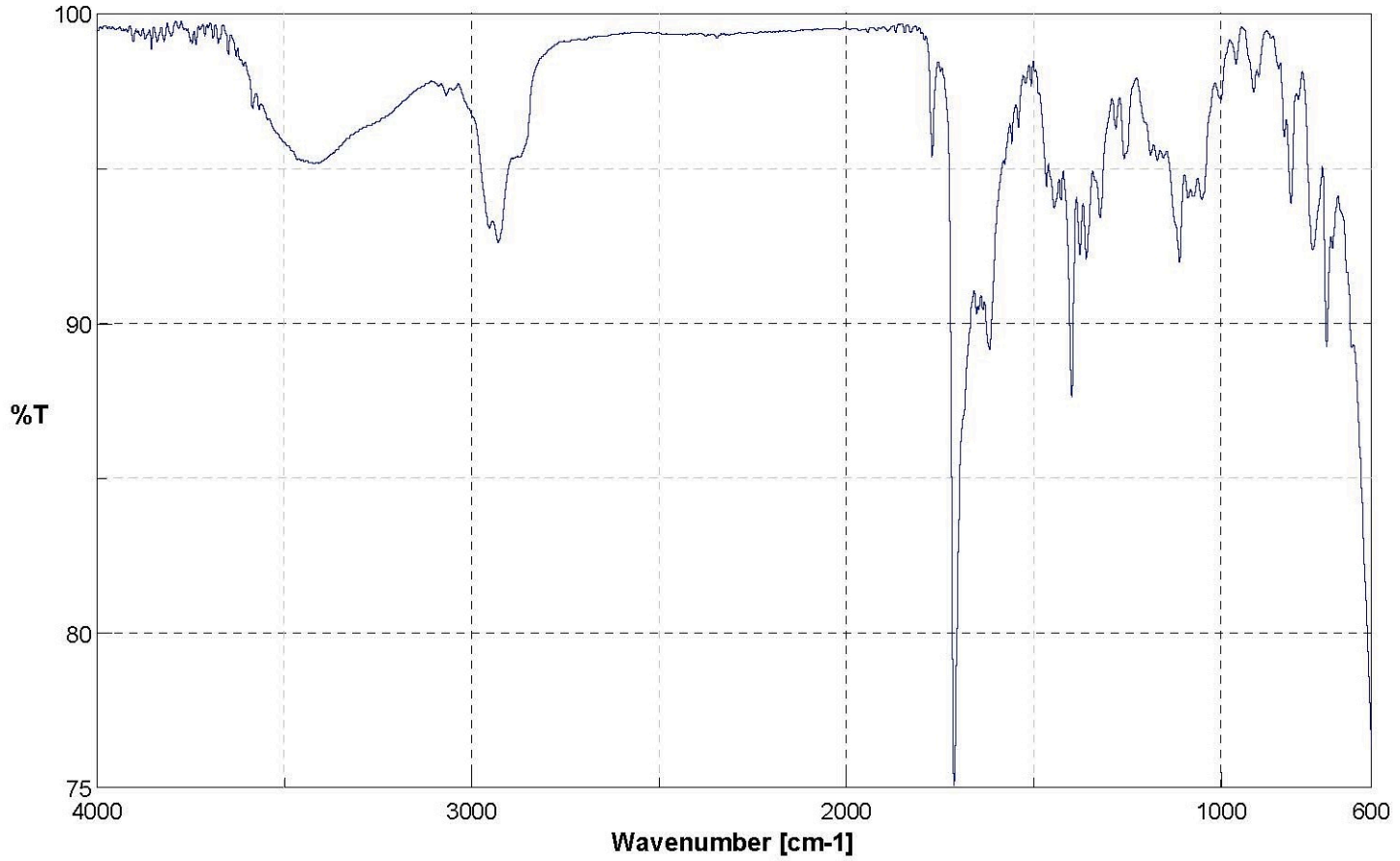



**Figure A2-87:** The Infrared Spectrum of Compound (+)-**3.46**

# Appendix 3: Spectra Relevant to Chapter 4

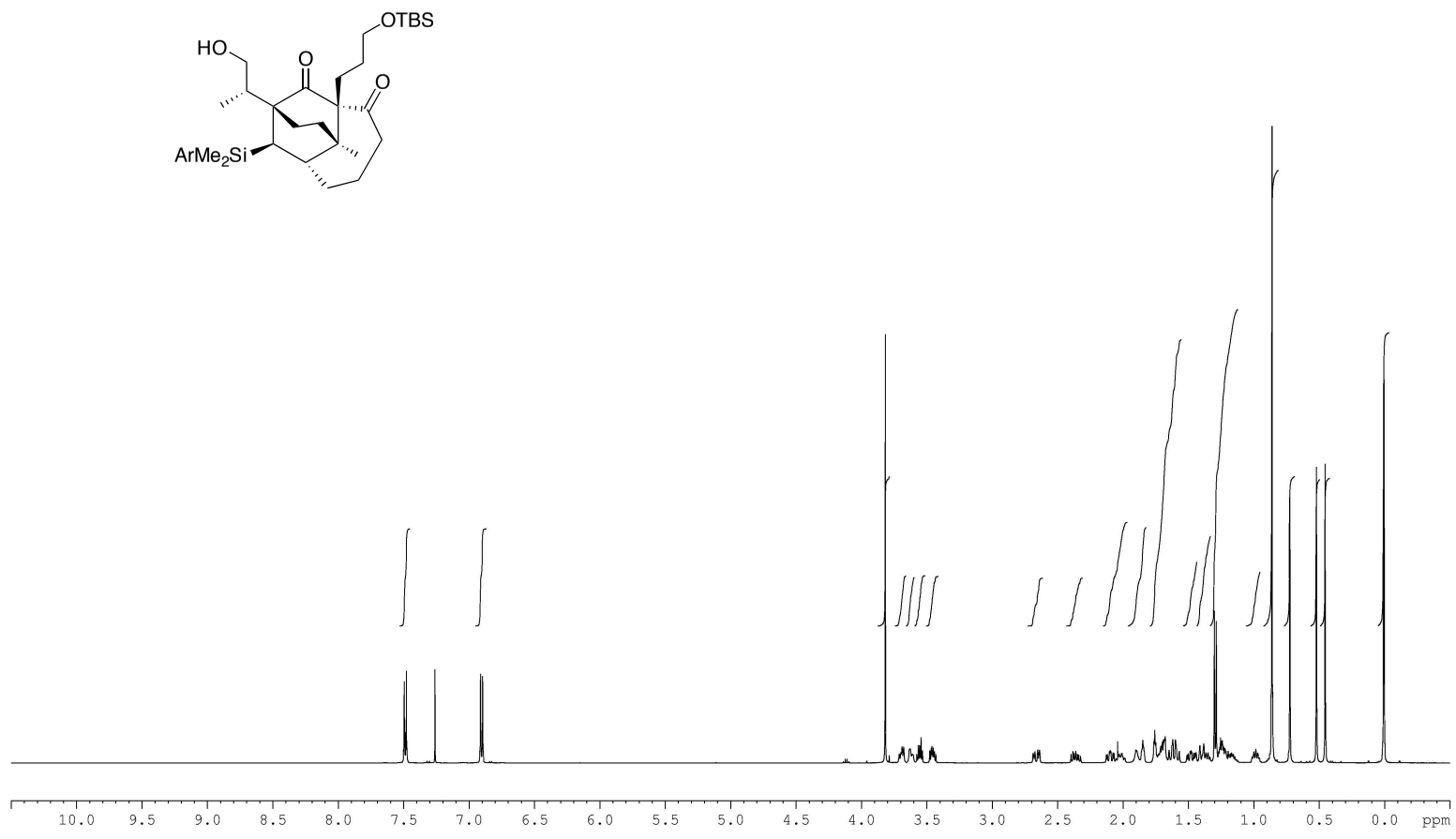



**Figure A3-1:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**4.3** in $CDCl_3$

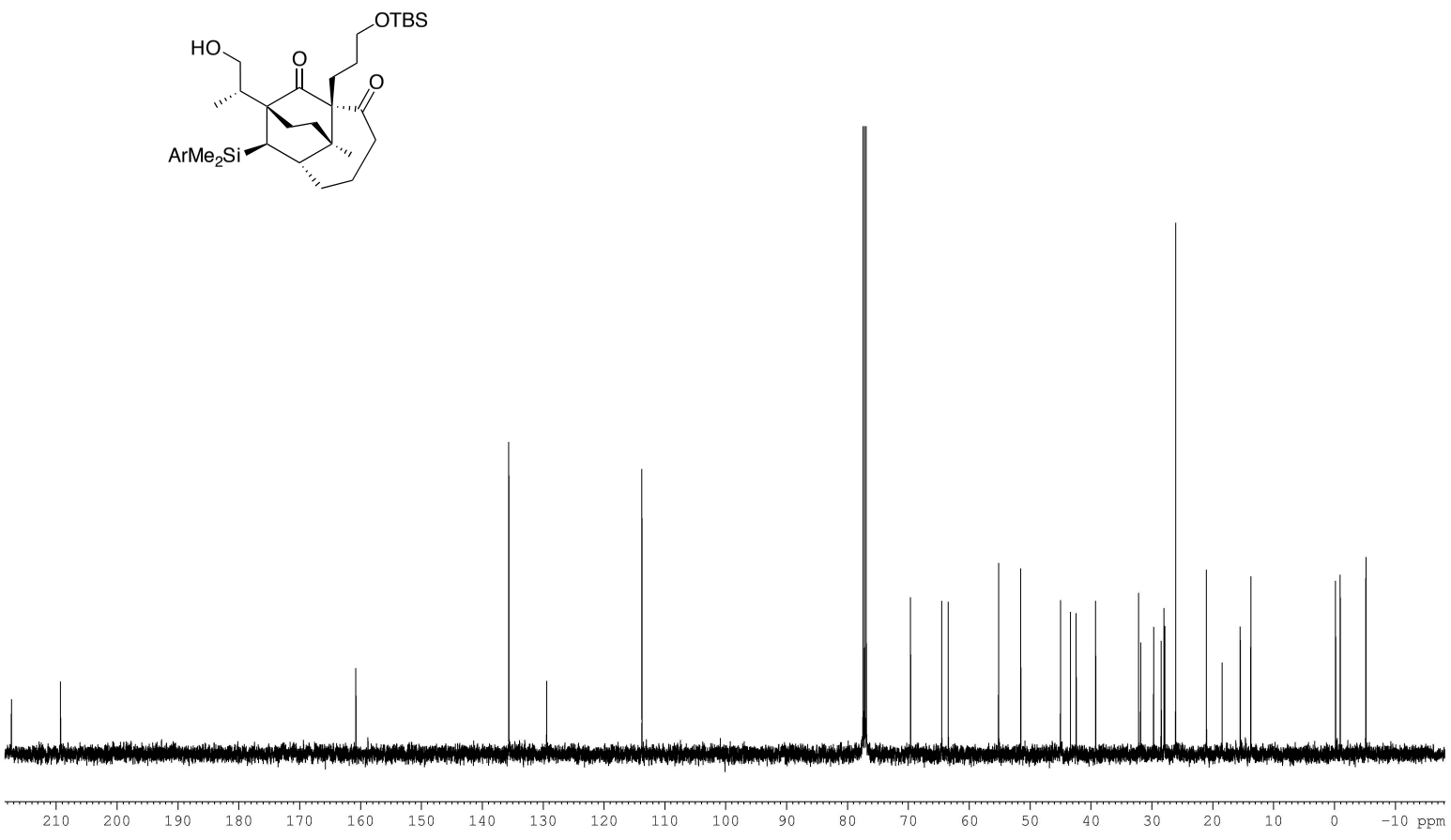



**Figure A3-2:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**4.3** in $CDCl_3$

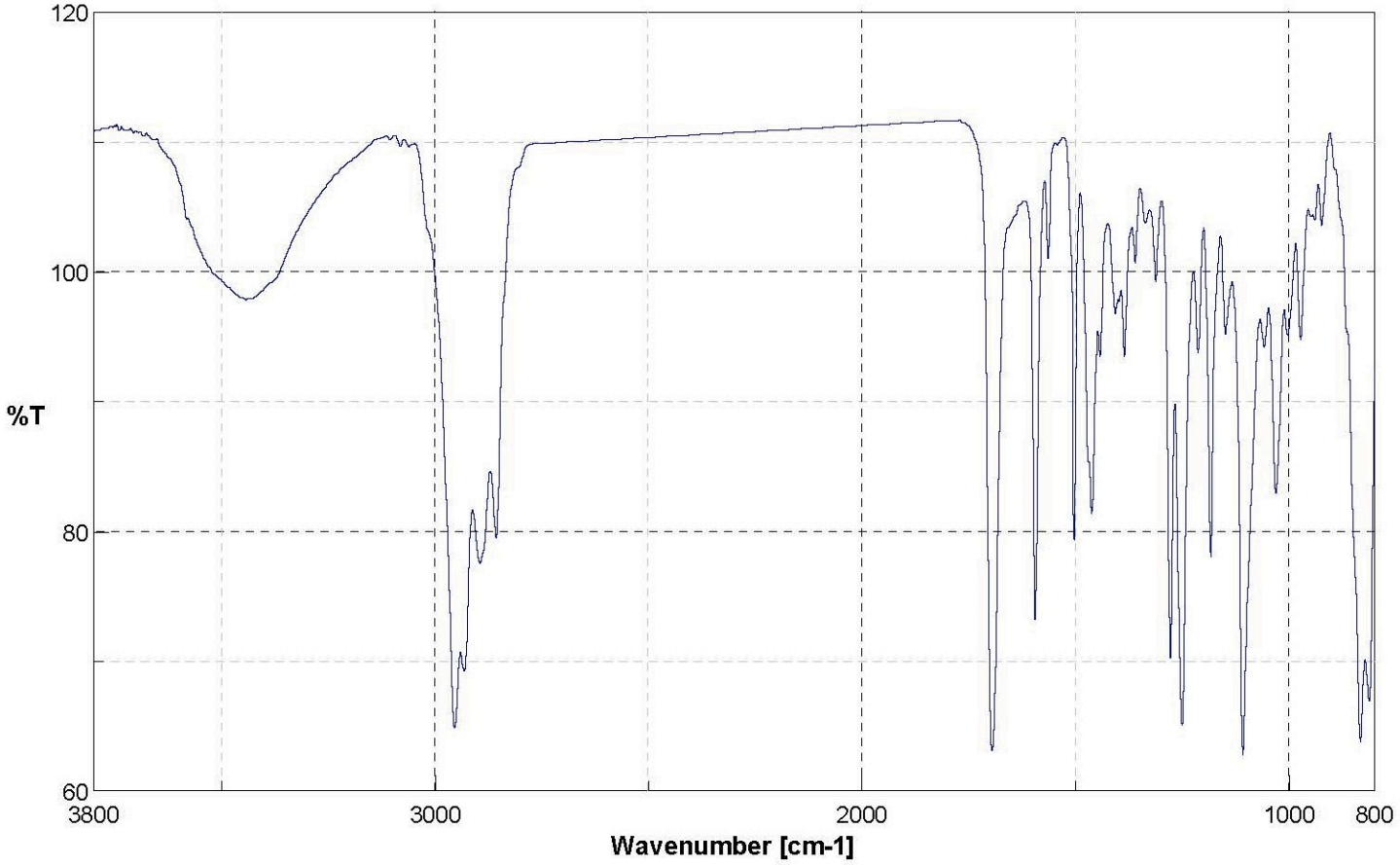



**Figure A3-3:** The Infrared Spectrum of Compound (+)-**4.3**

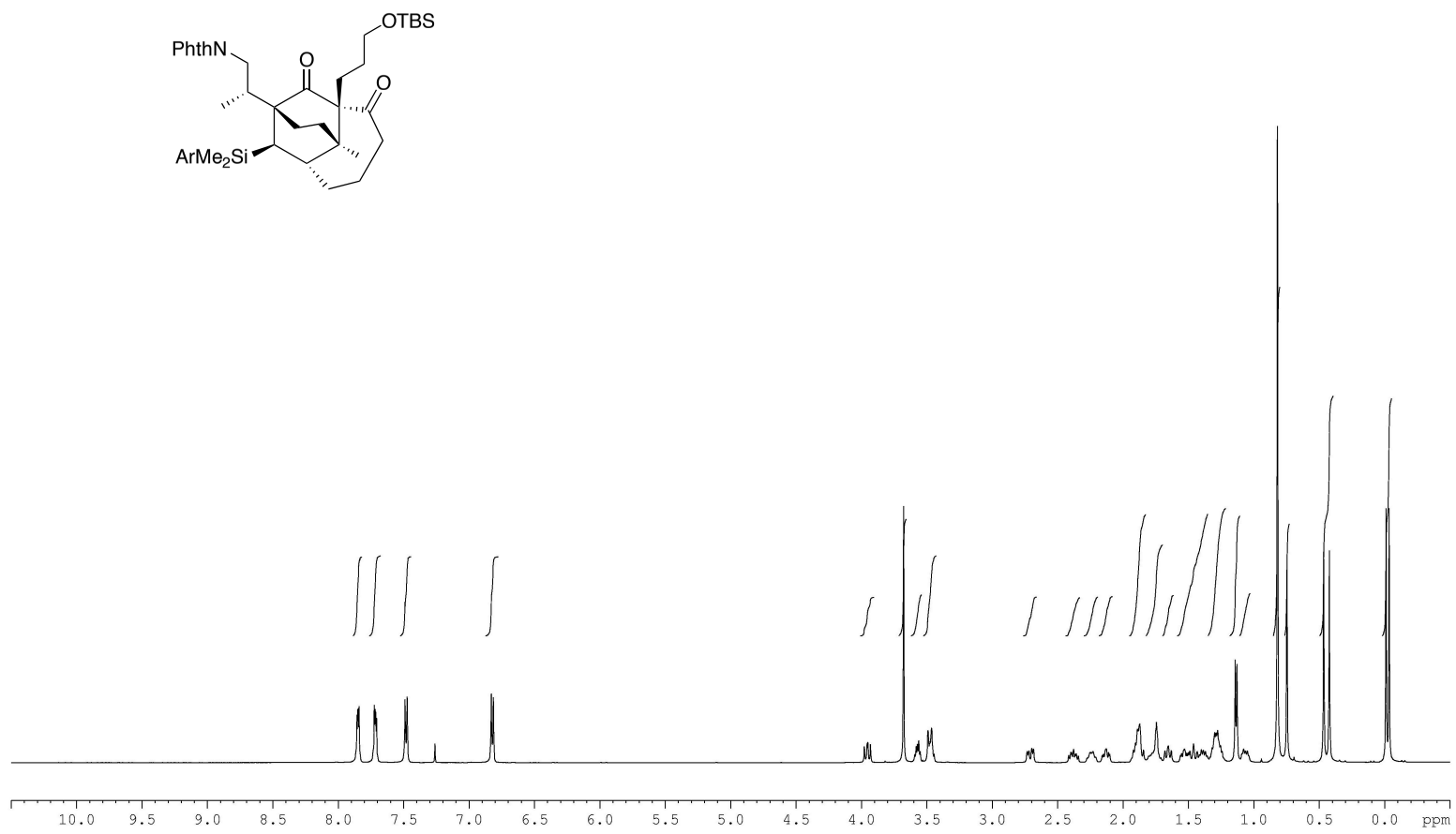



**Figure A3-4:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**4.4** in $CDCl_3$

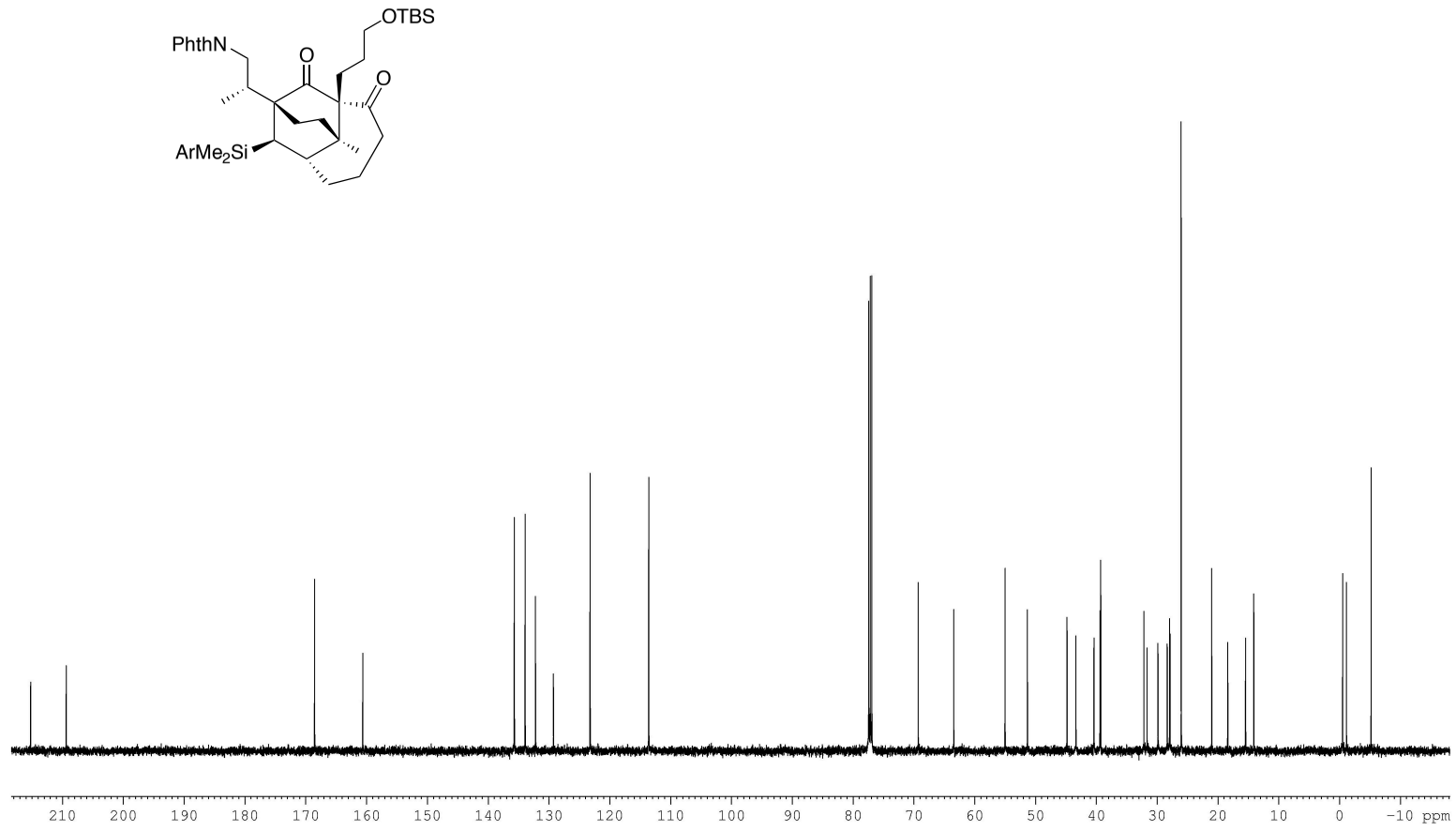



**Figure A3-5:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**4.4** in $CDCl_3$

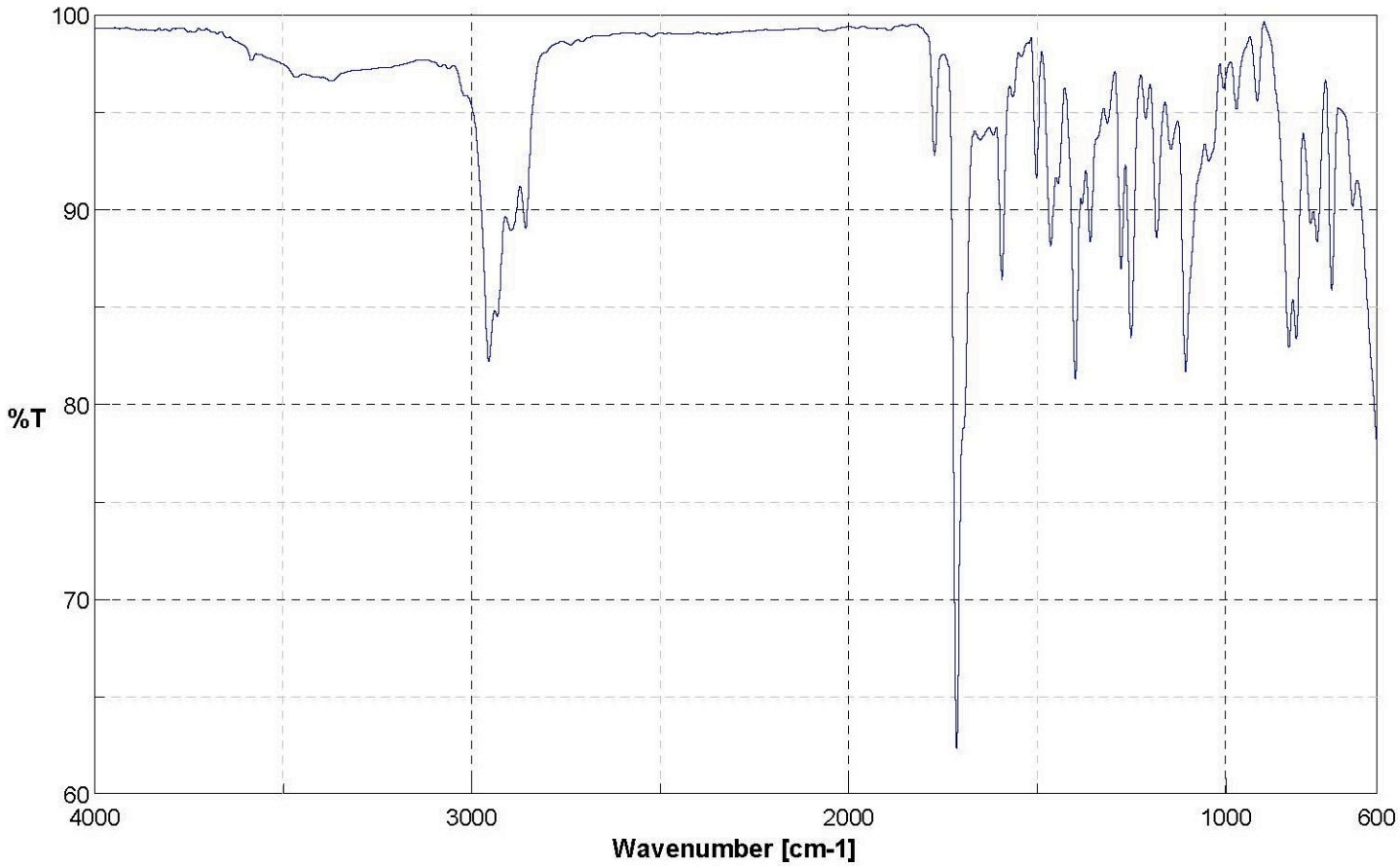



**Figure A3-6:** The Infrared Spectrum of Compound (+)-**4.4**

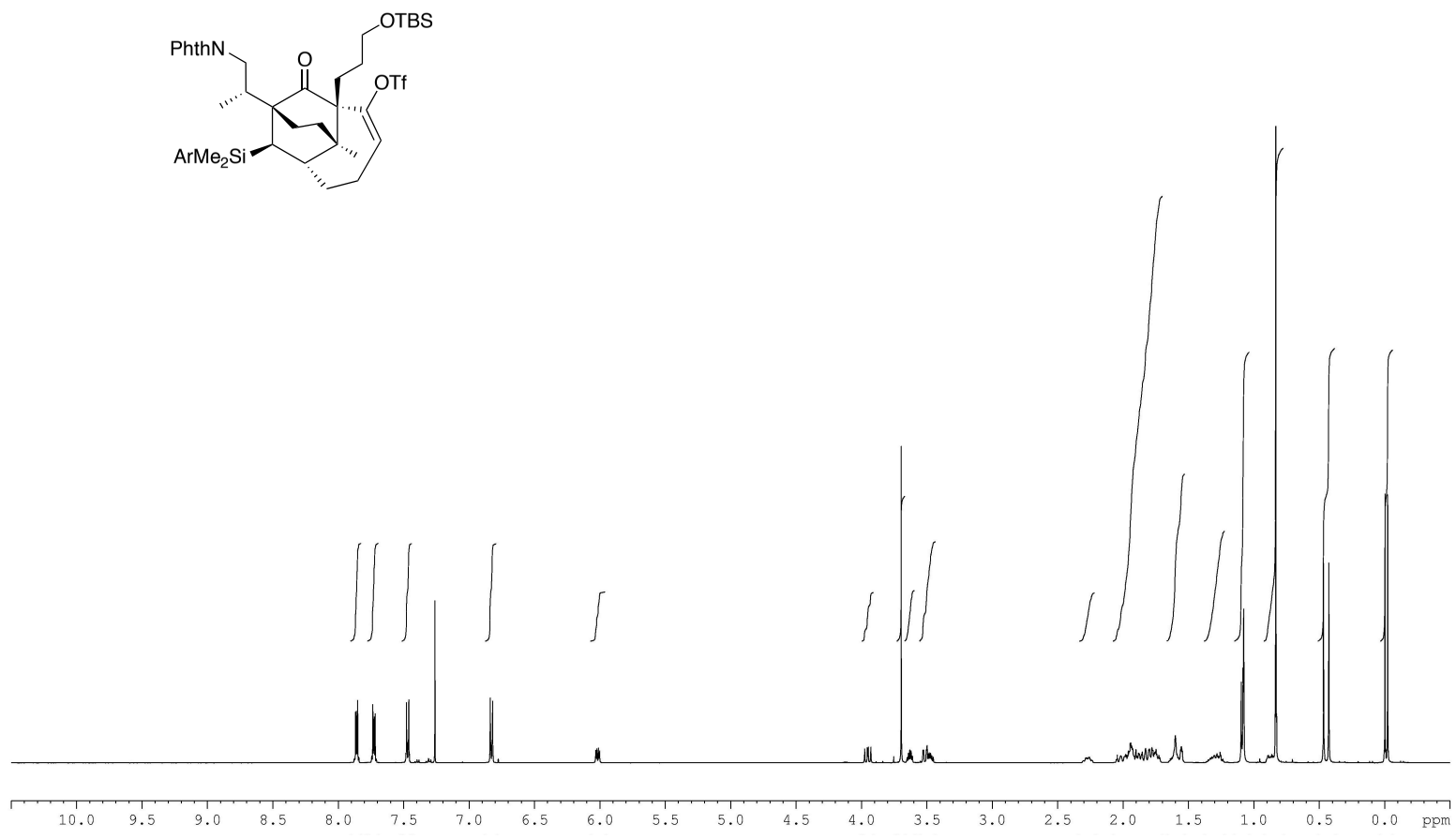



**Figure A3-7:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**4.5** in $CDCl_3$

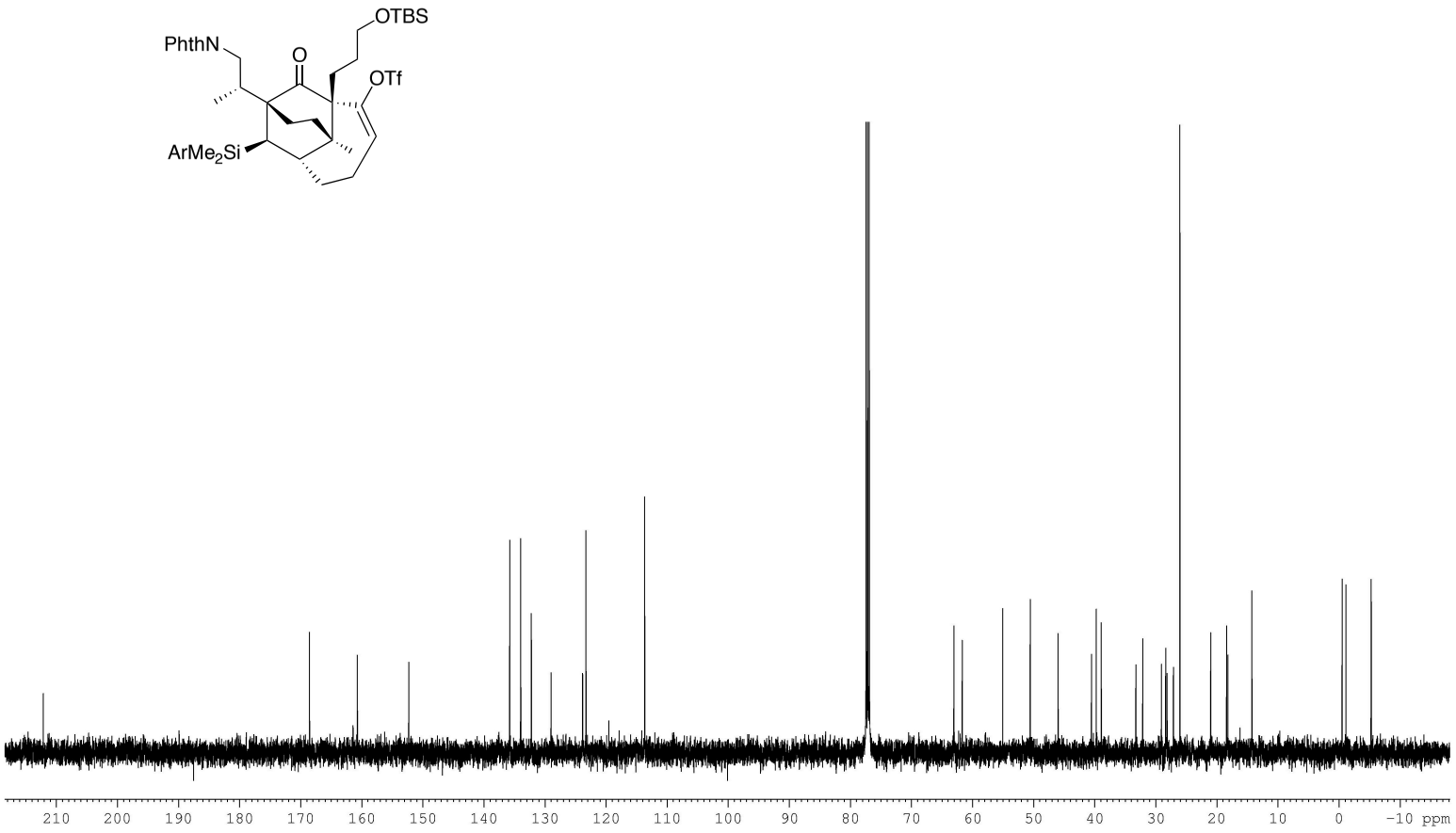



**Figure A3-8:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**4.5** in $CDCl_3$

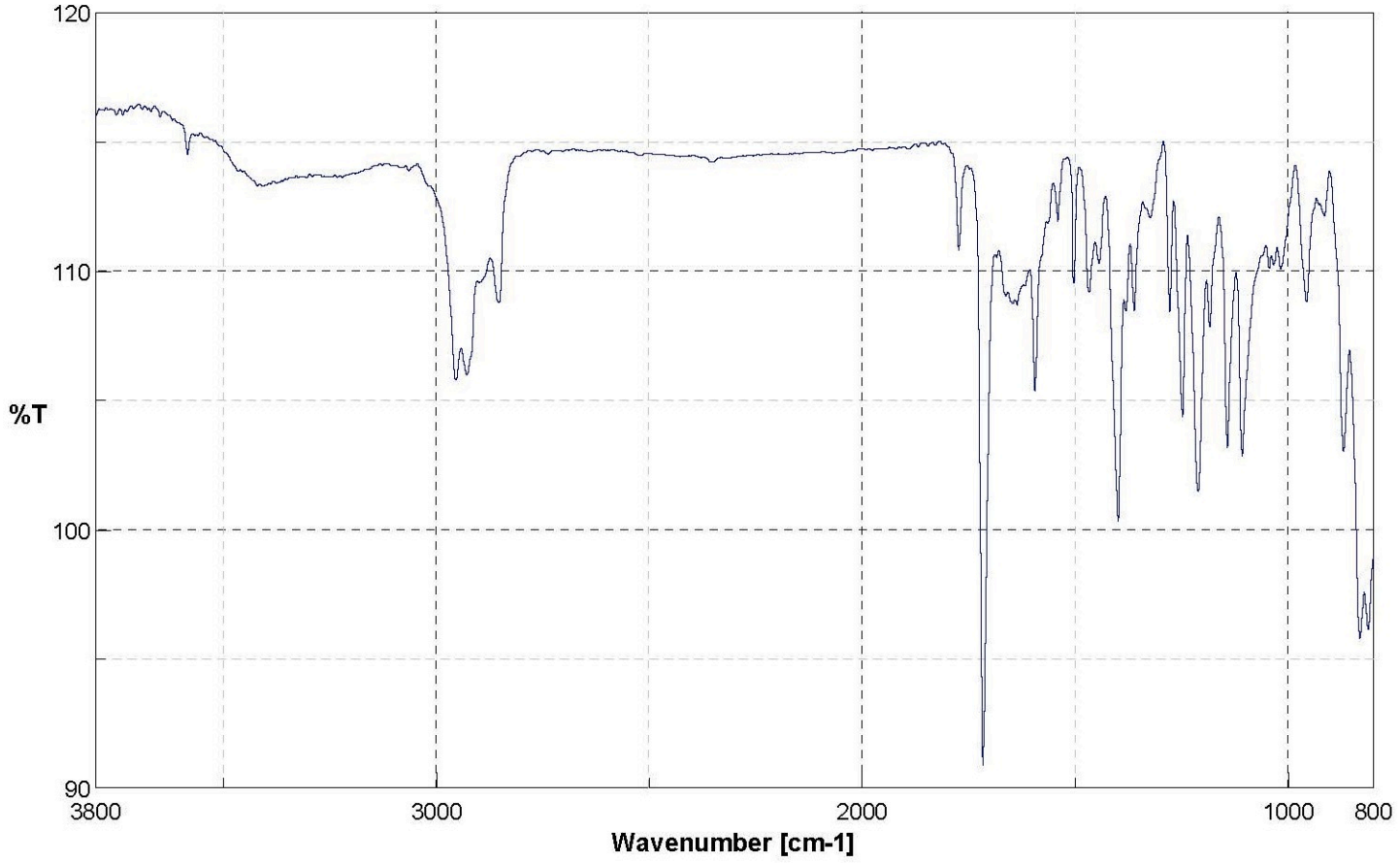



**Figure A3-9:** The Infrared Spectrum of Compound (+)-**4.5**

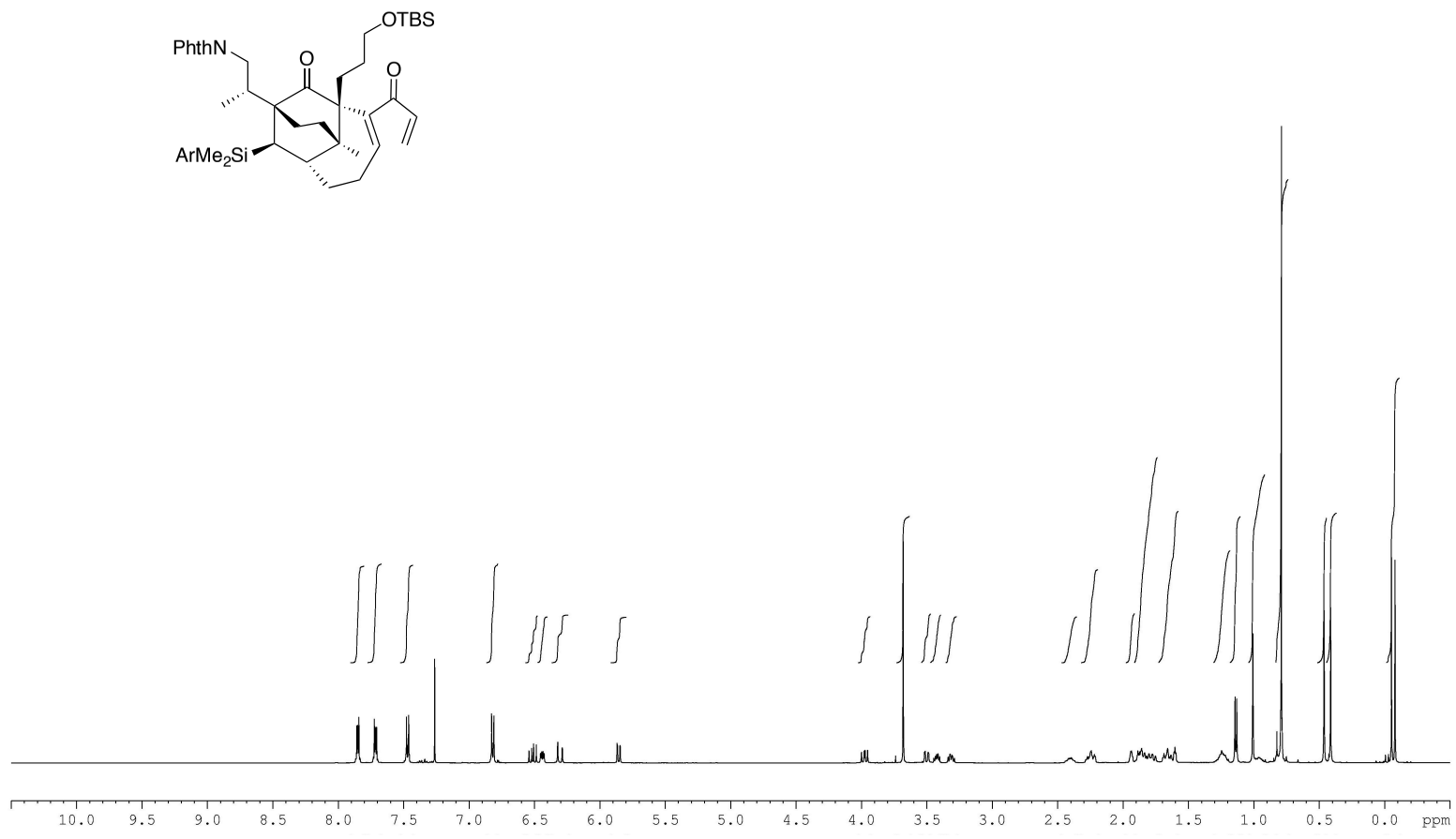



**Figure A3-10:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**4.6** in $CDCl_3$

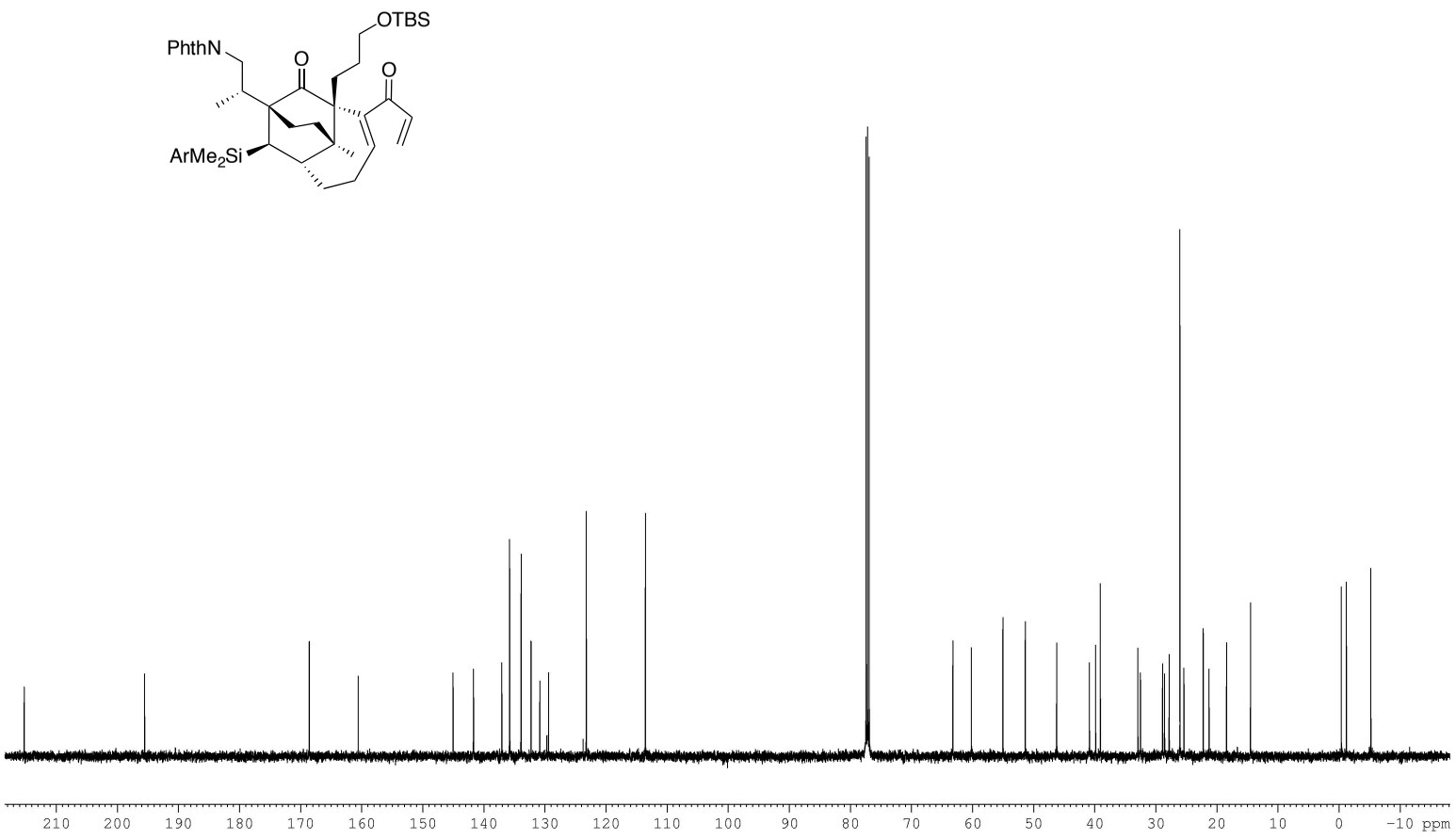



**Figure A3-11:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**4.6** in $CDCl_3$

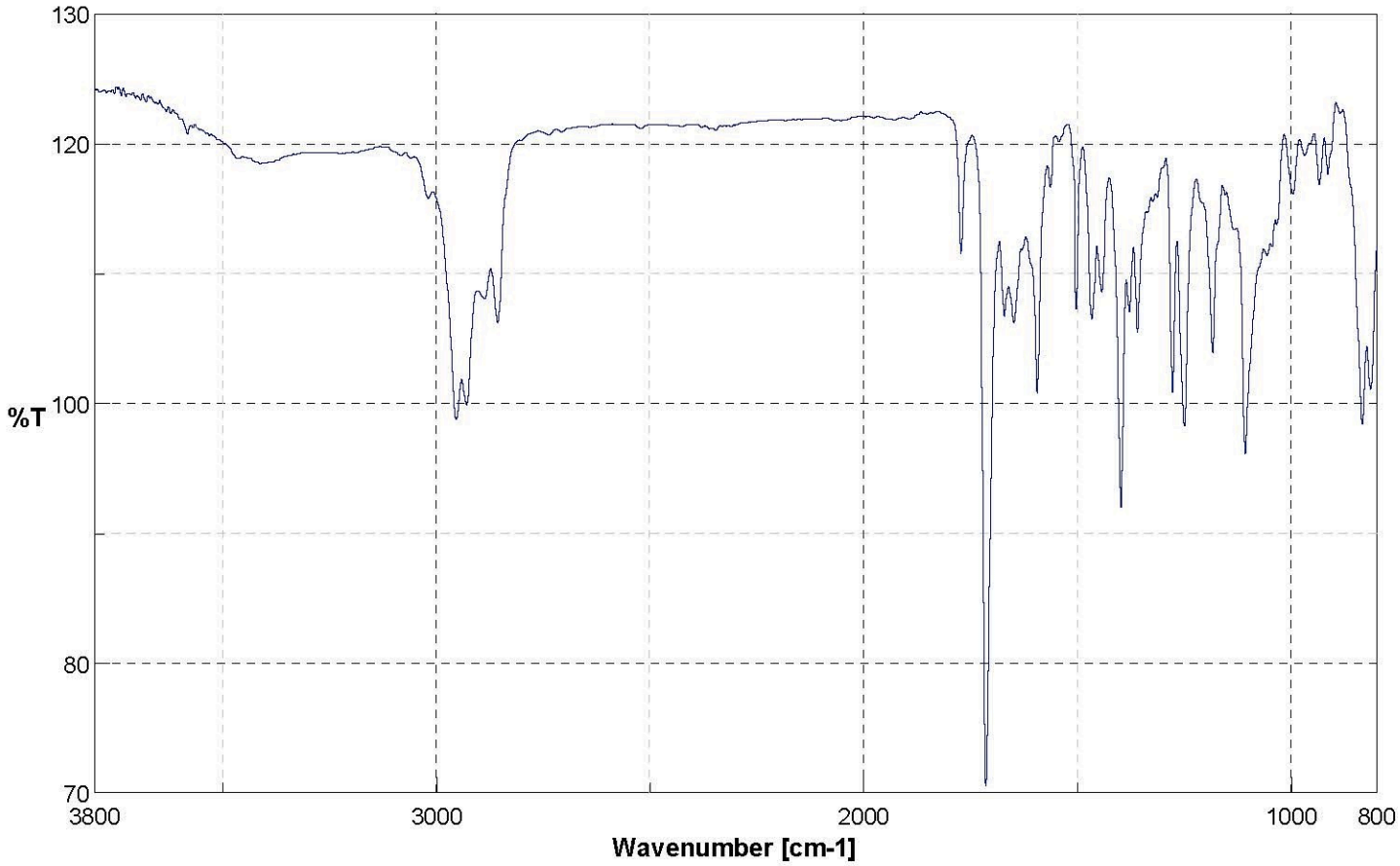



**Figure A3-12:** The Infrared Spectrum of Compound (+)-**4.6**

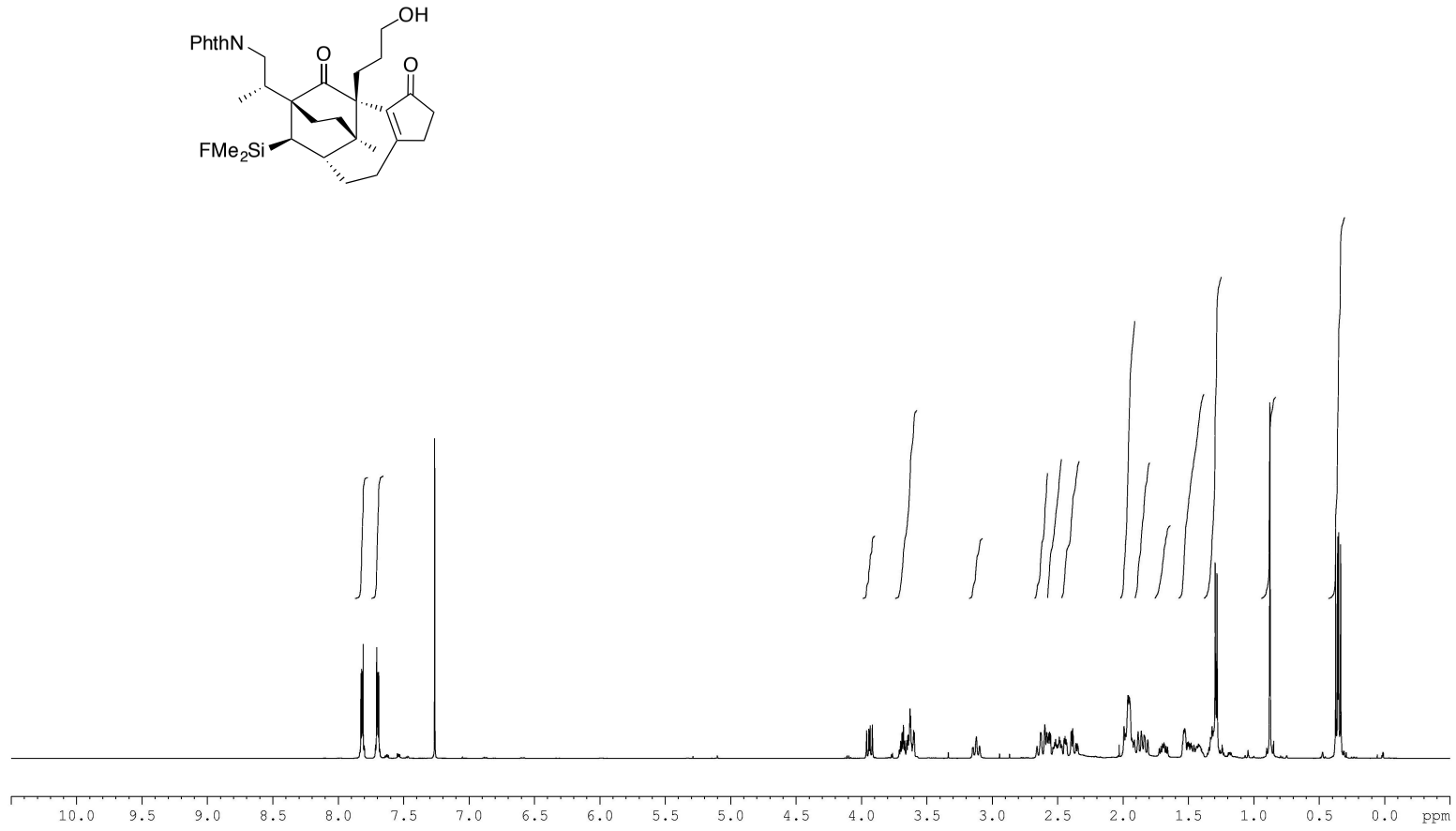



**Figure A3-13:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.47** in $CDCl_3$

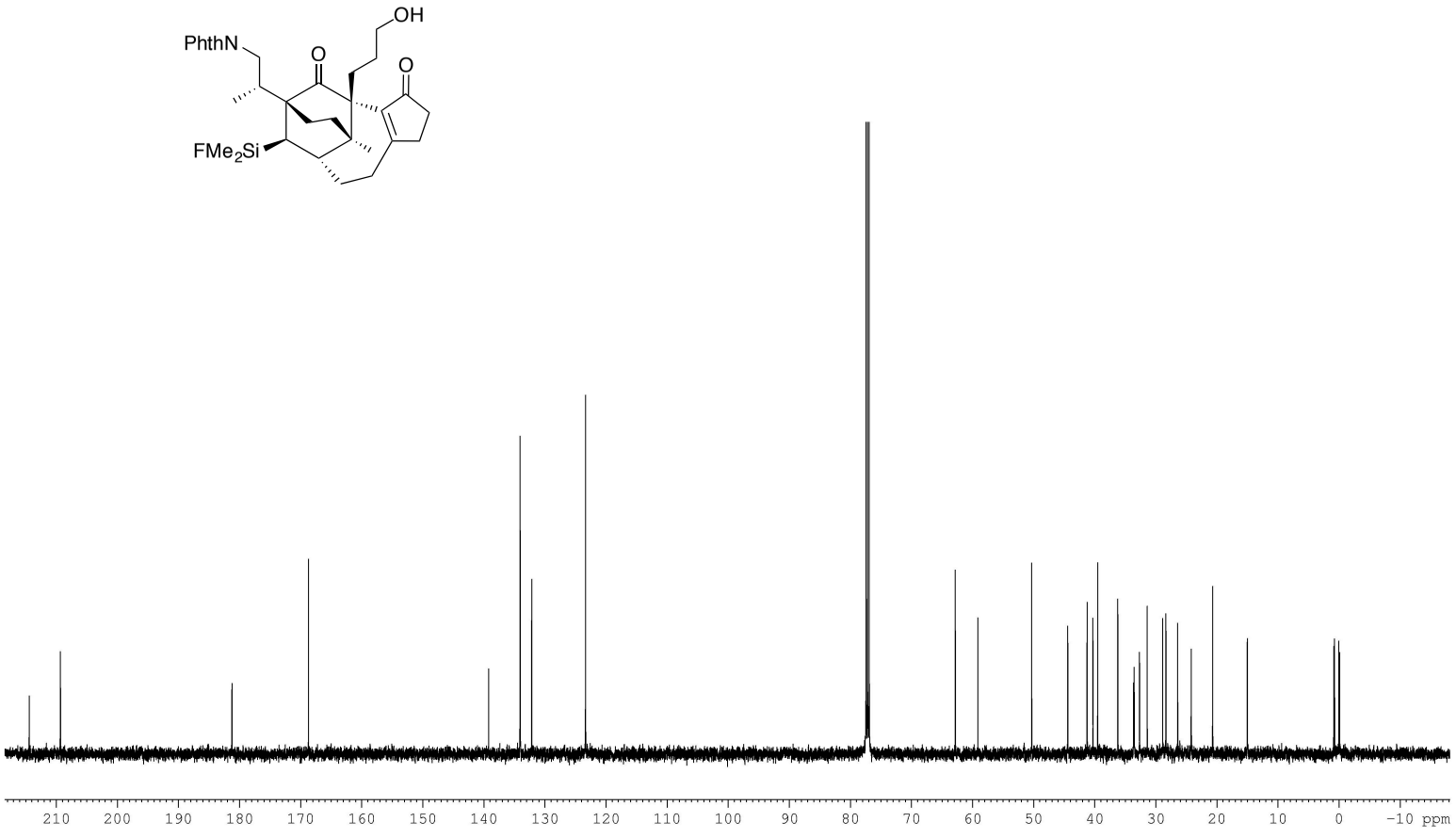



**Figure A3-14:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.47** in $CDCl_3$

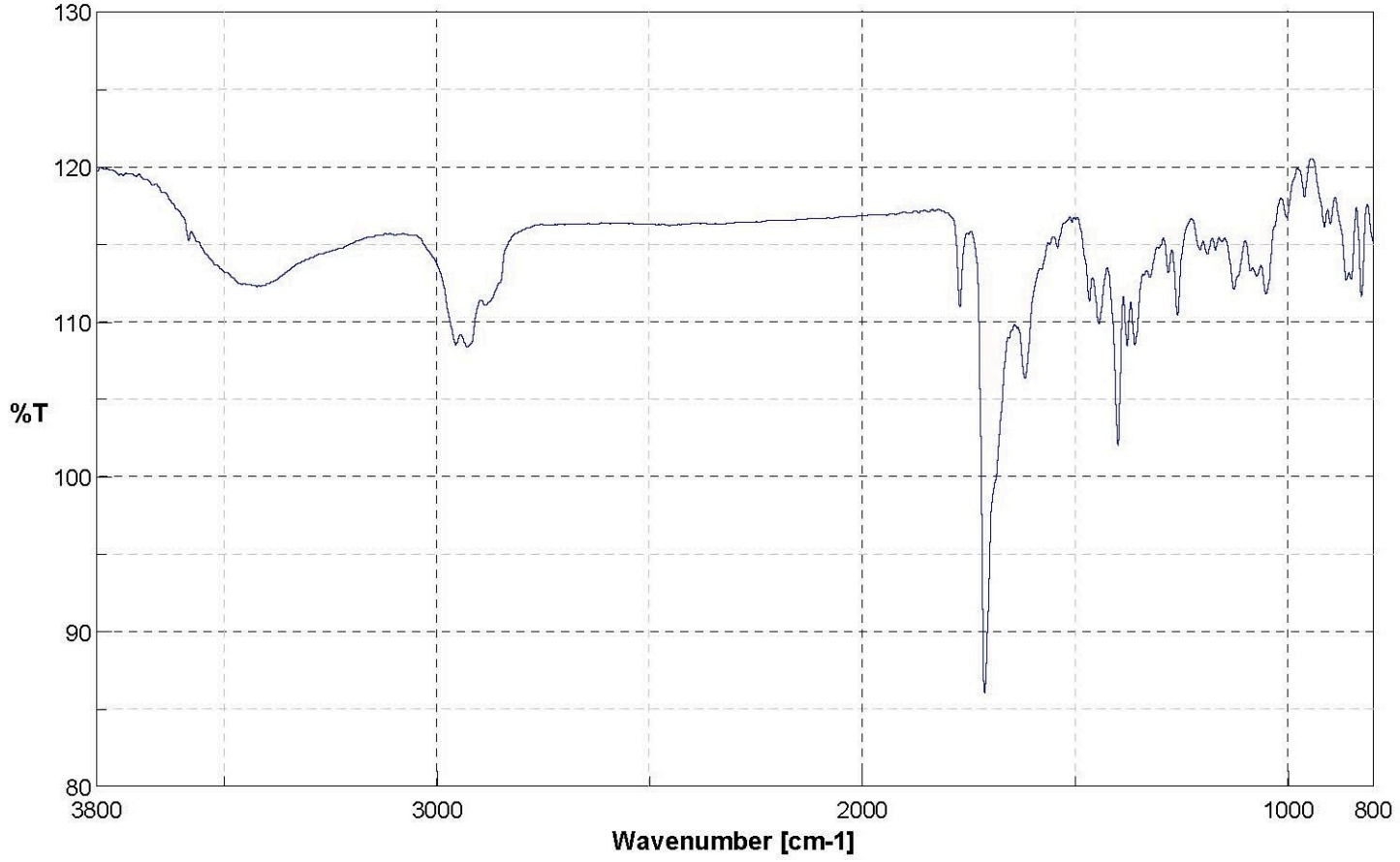



**Figure A3-15:** The Infrared Spectrum of Compound (+)-**3.47**

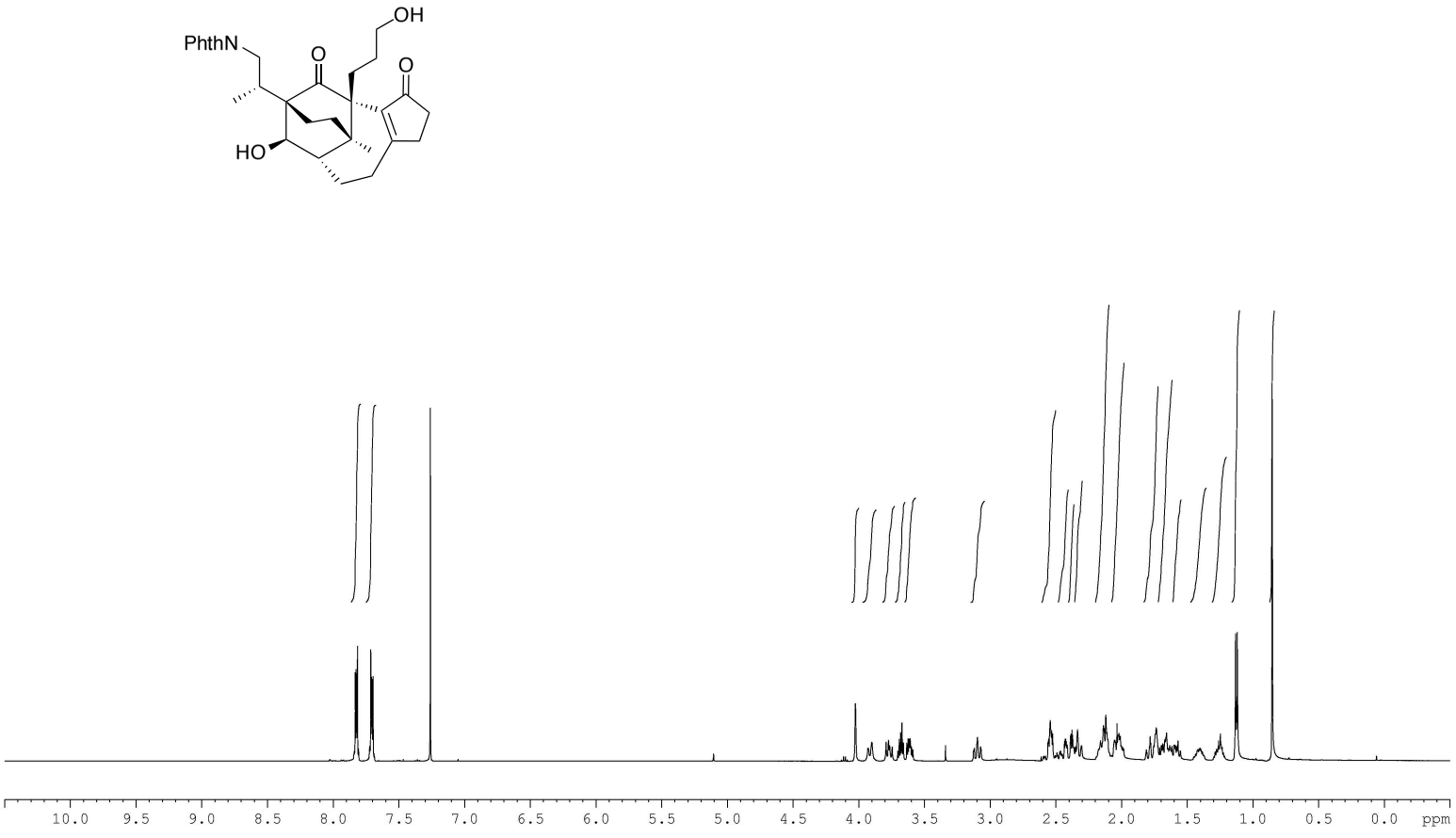



**Figure A3-16:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**3.48** in $CDCl_3$

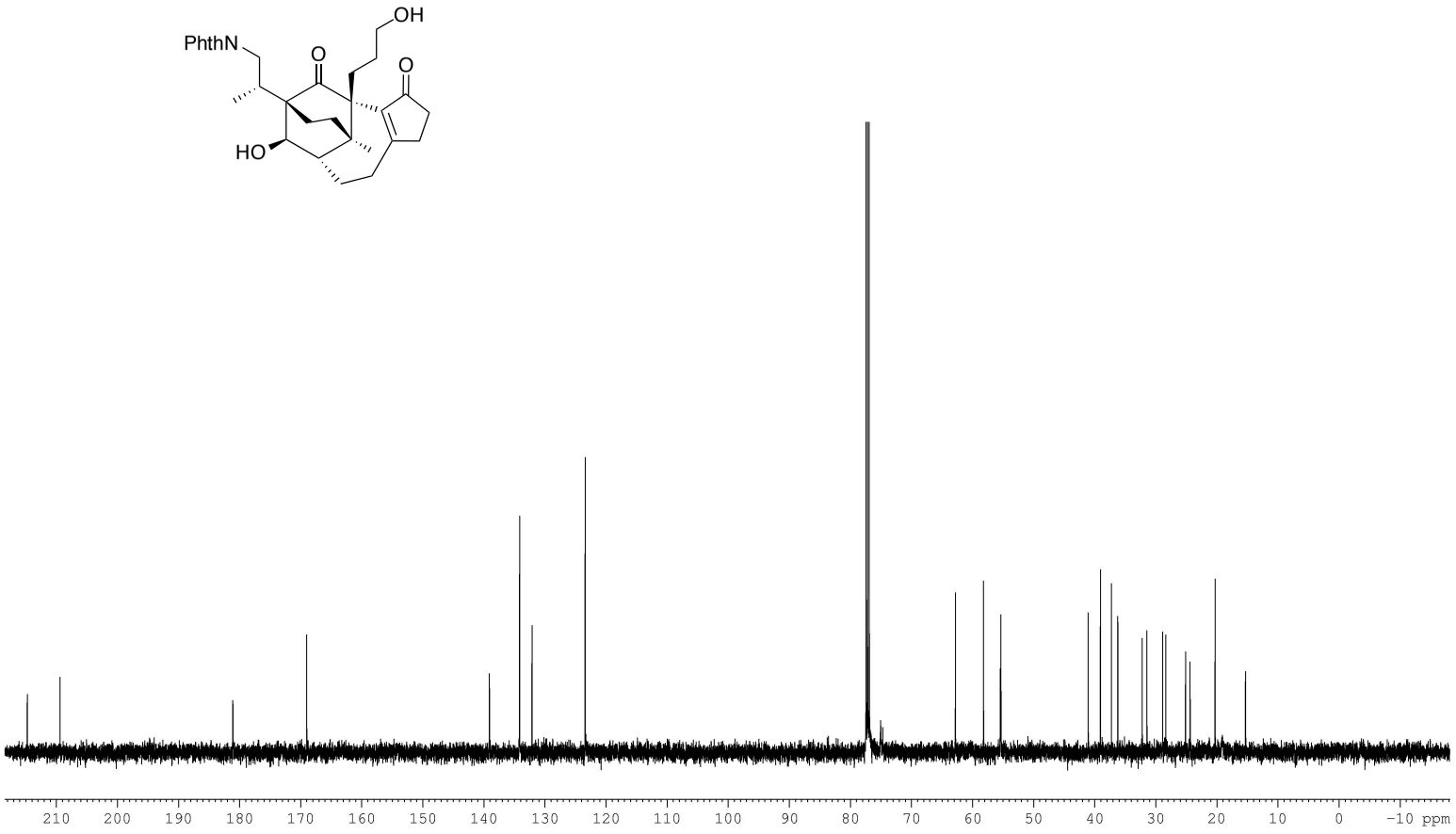



**Figure A3-17:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**3.48** in $CDCl_3$

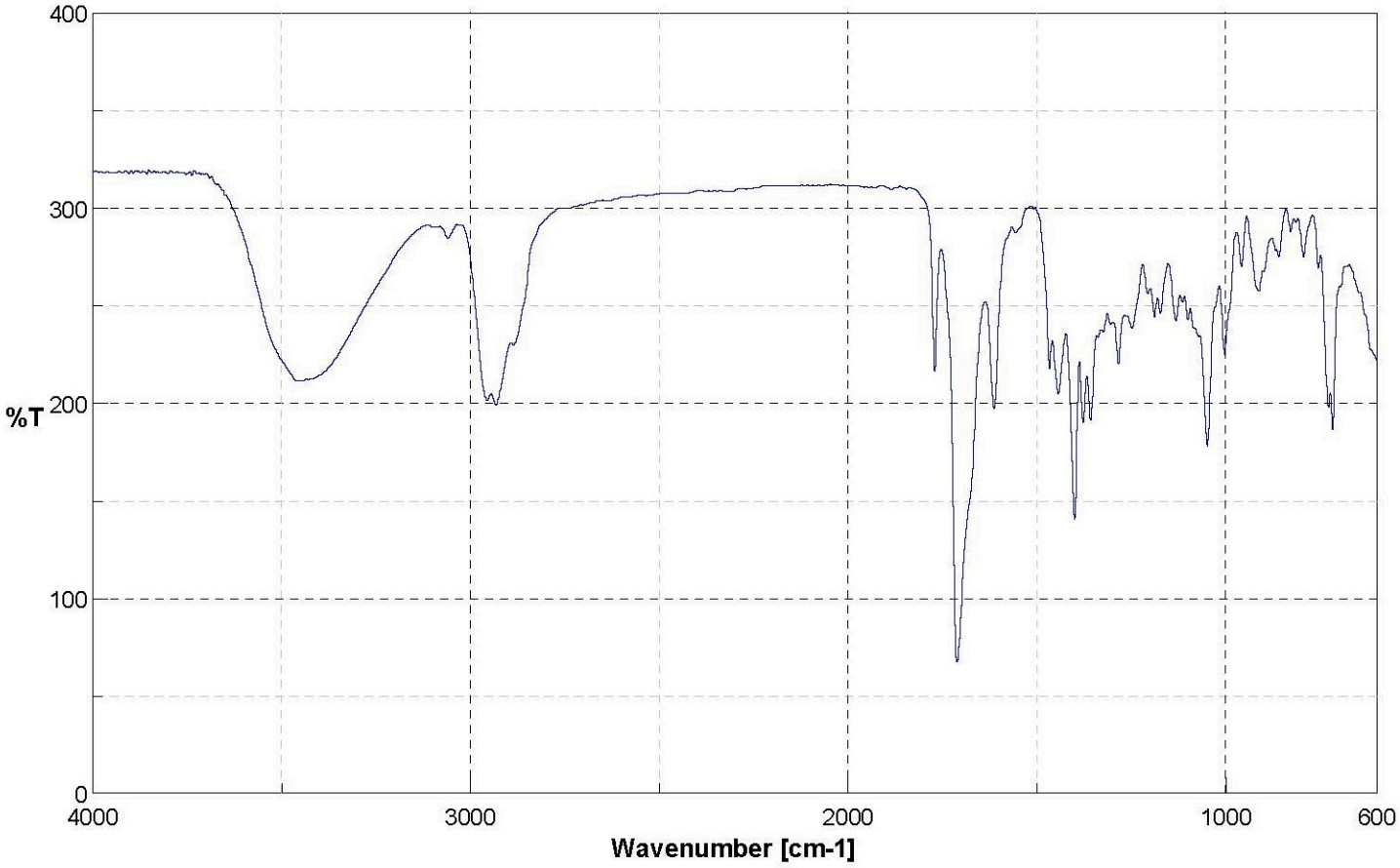



**Figure A3-18:** The Infrared Spectrum of Compound (+)-**3.48**

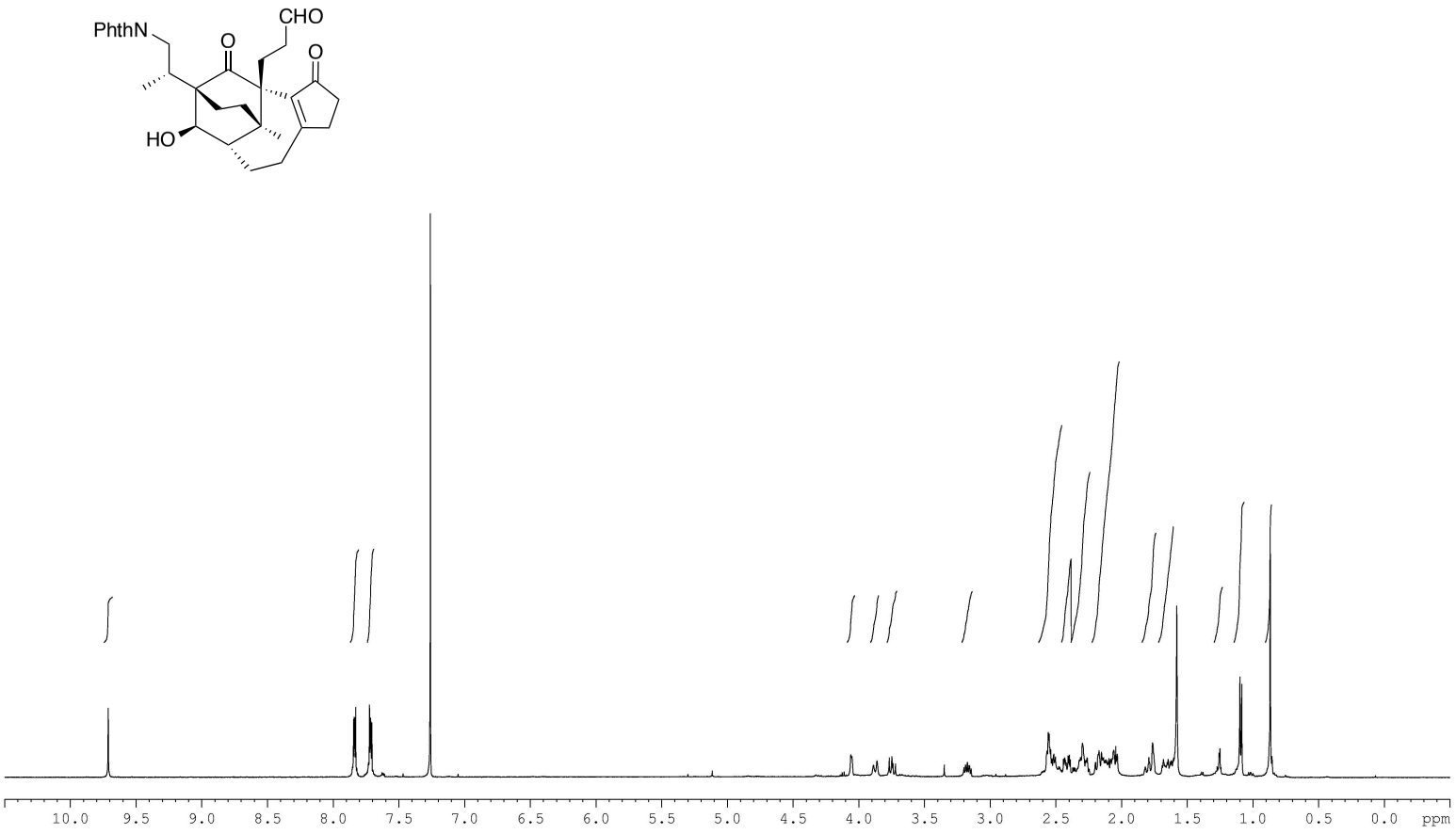



**Figure A3-19:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**4.7** in $CDCl_3$

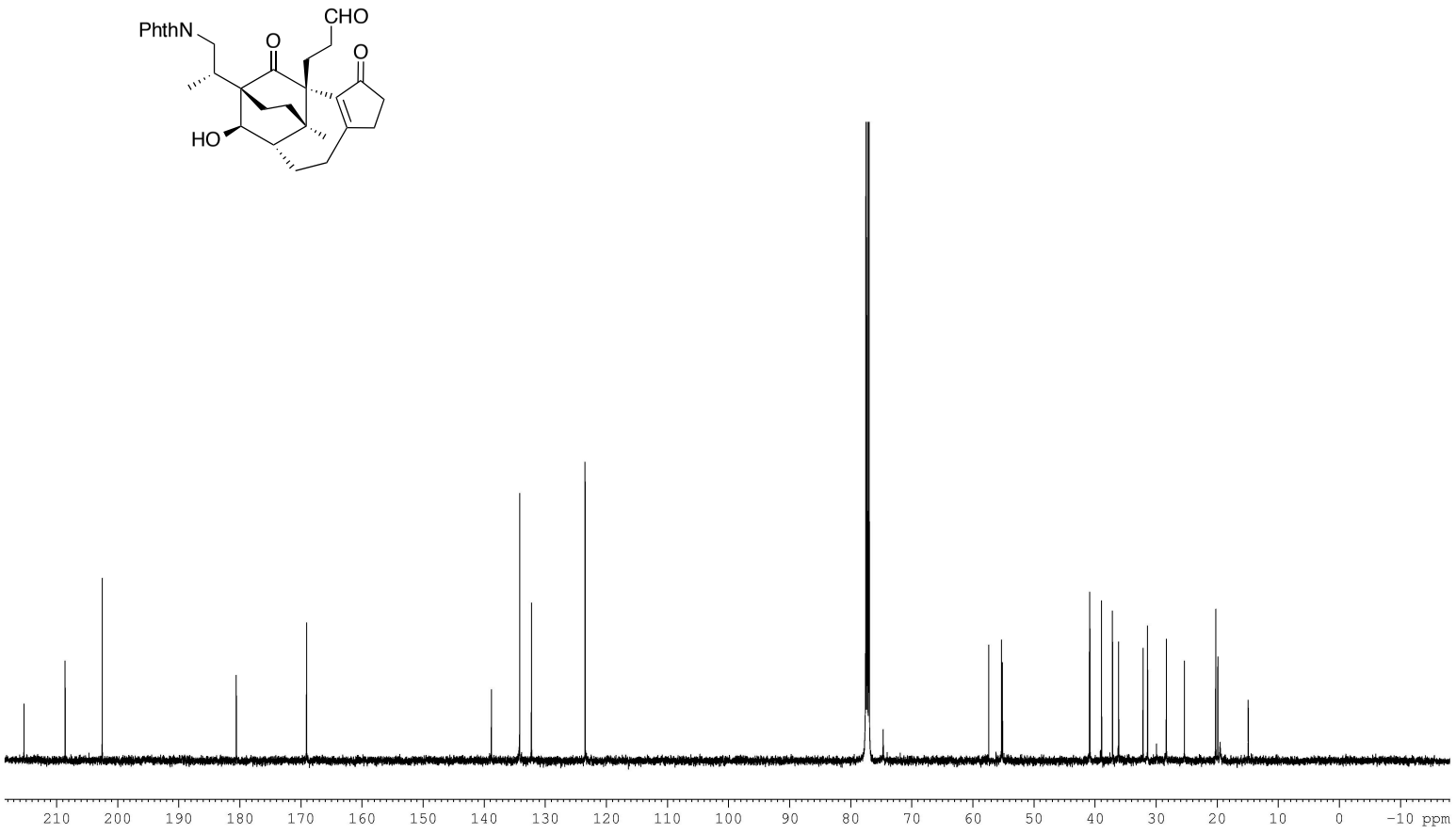



**Figure A3-20:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**4.7** in $CDCl_3$

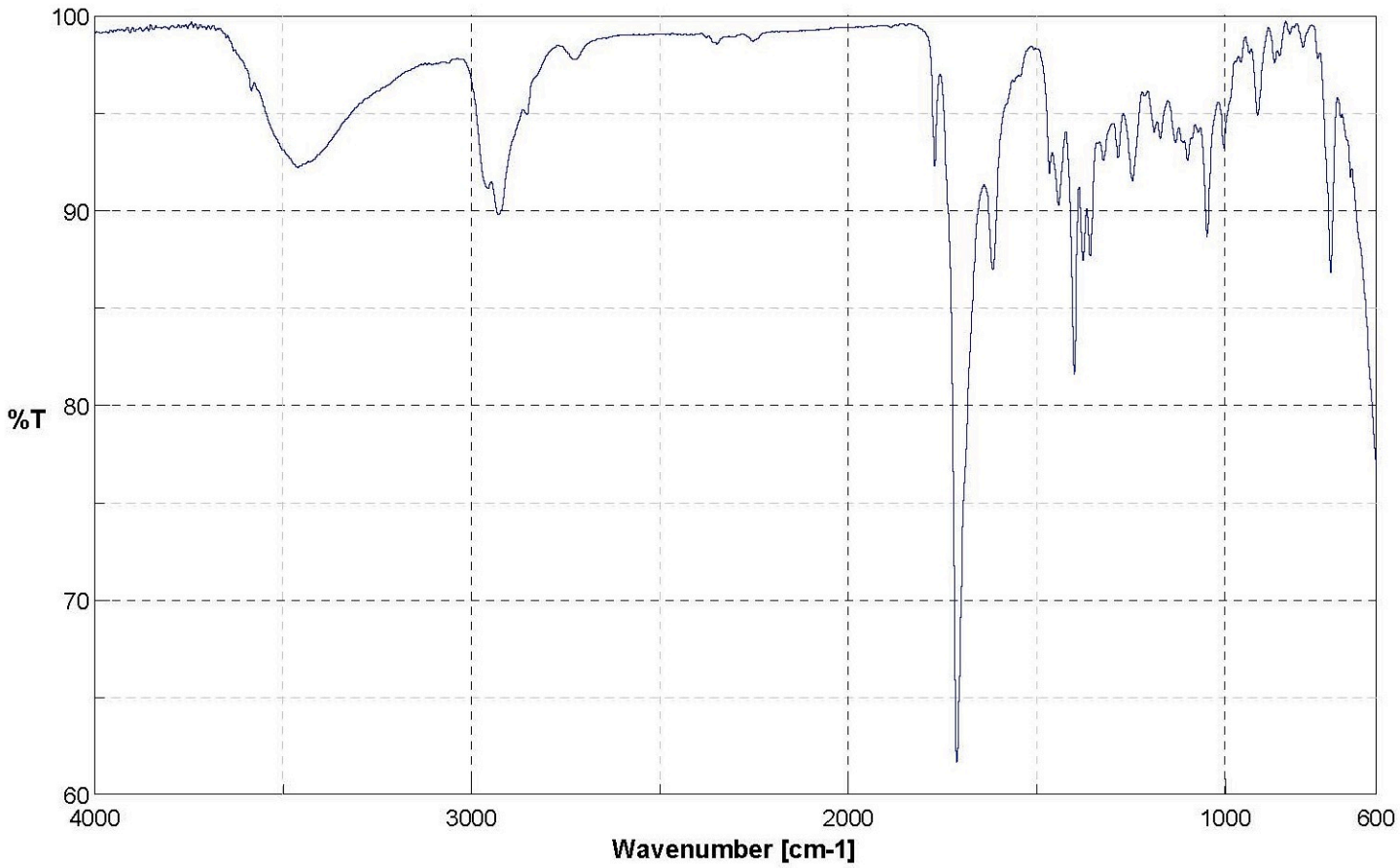



**Figure A3-21:** The Infrared Spectrum of Comopund (+)-**4.7**

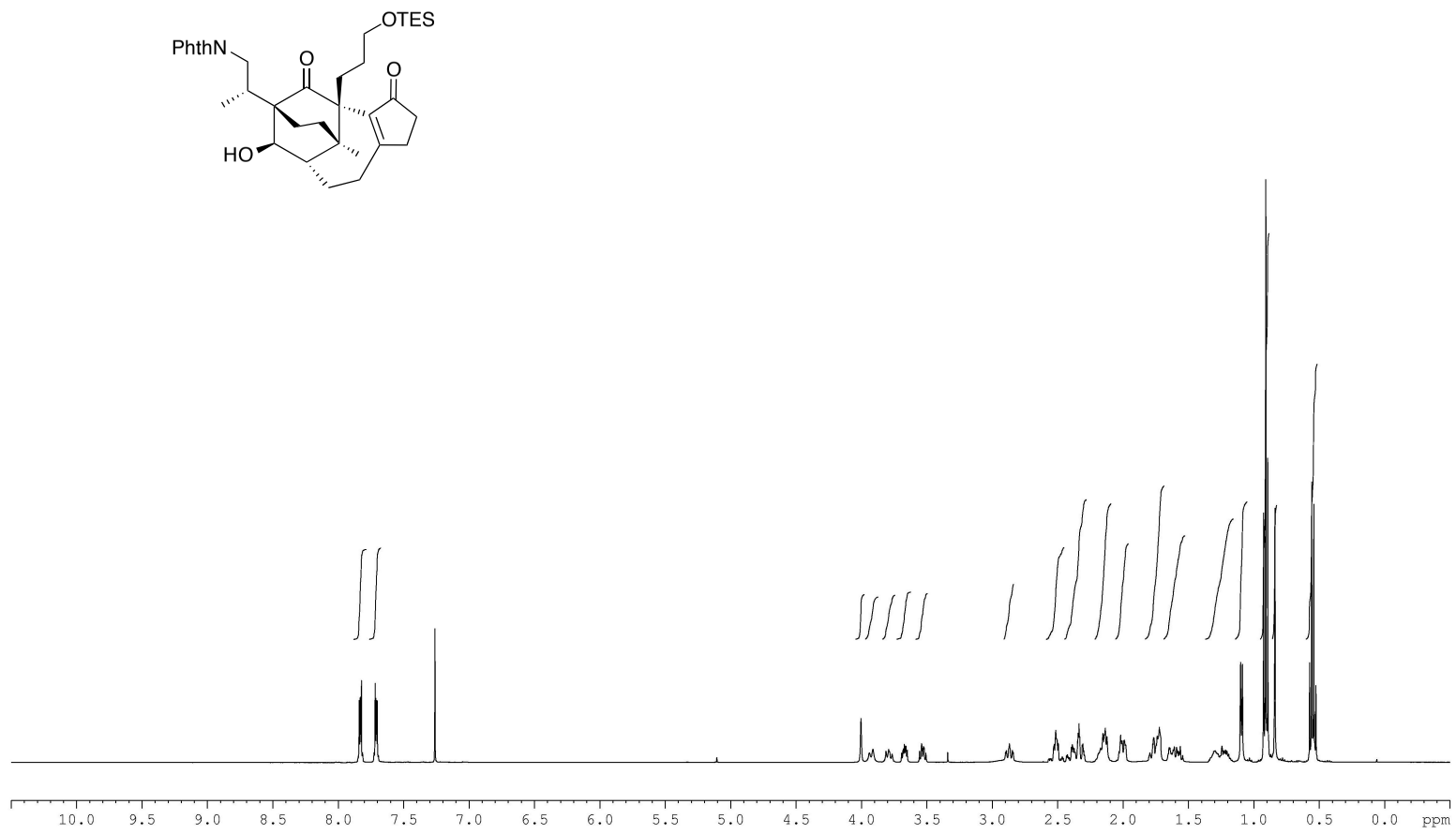



**Figure A3-22:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**4.9** in $CDCl_3$

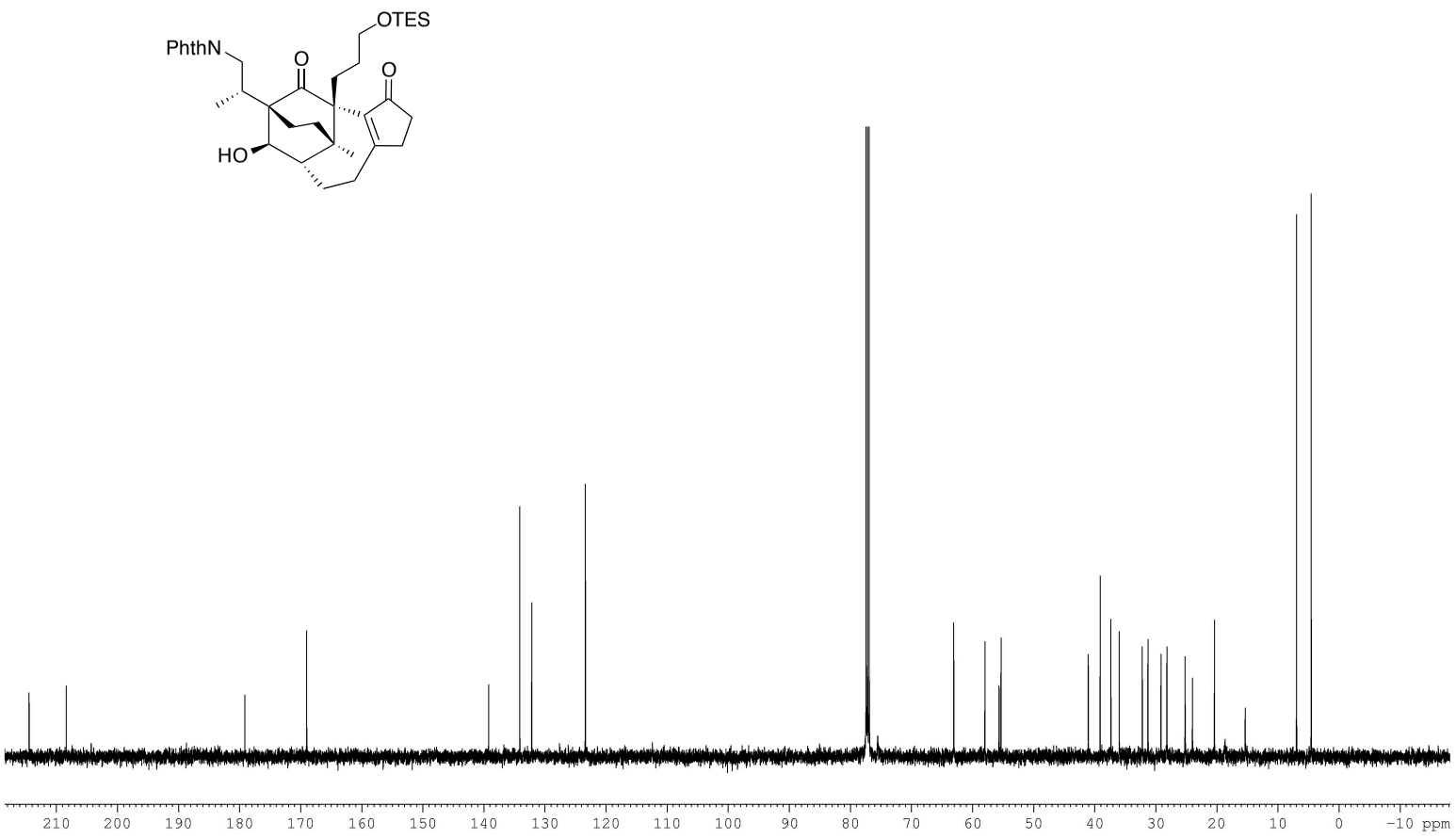



**Figure A3-23:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**4.9** in $CDCl_3$

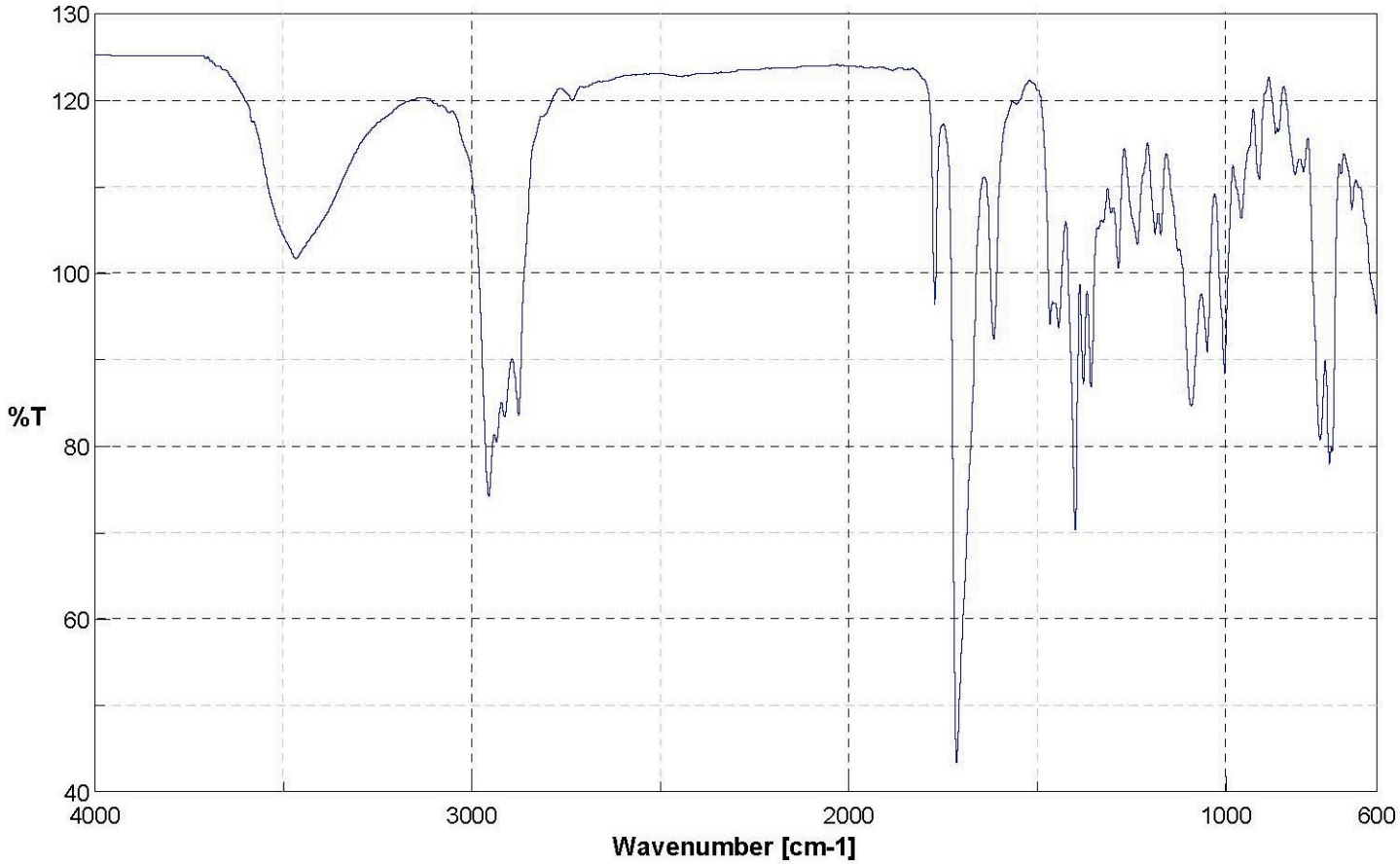



**Figure A3-24:** The Infrared Spectrum of Compound (+)-**4.9**

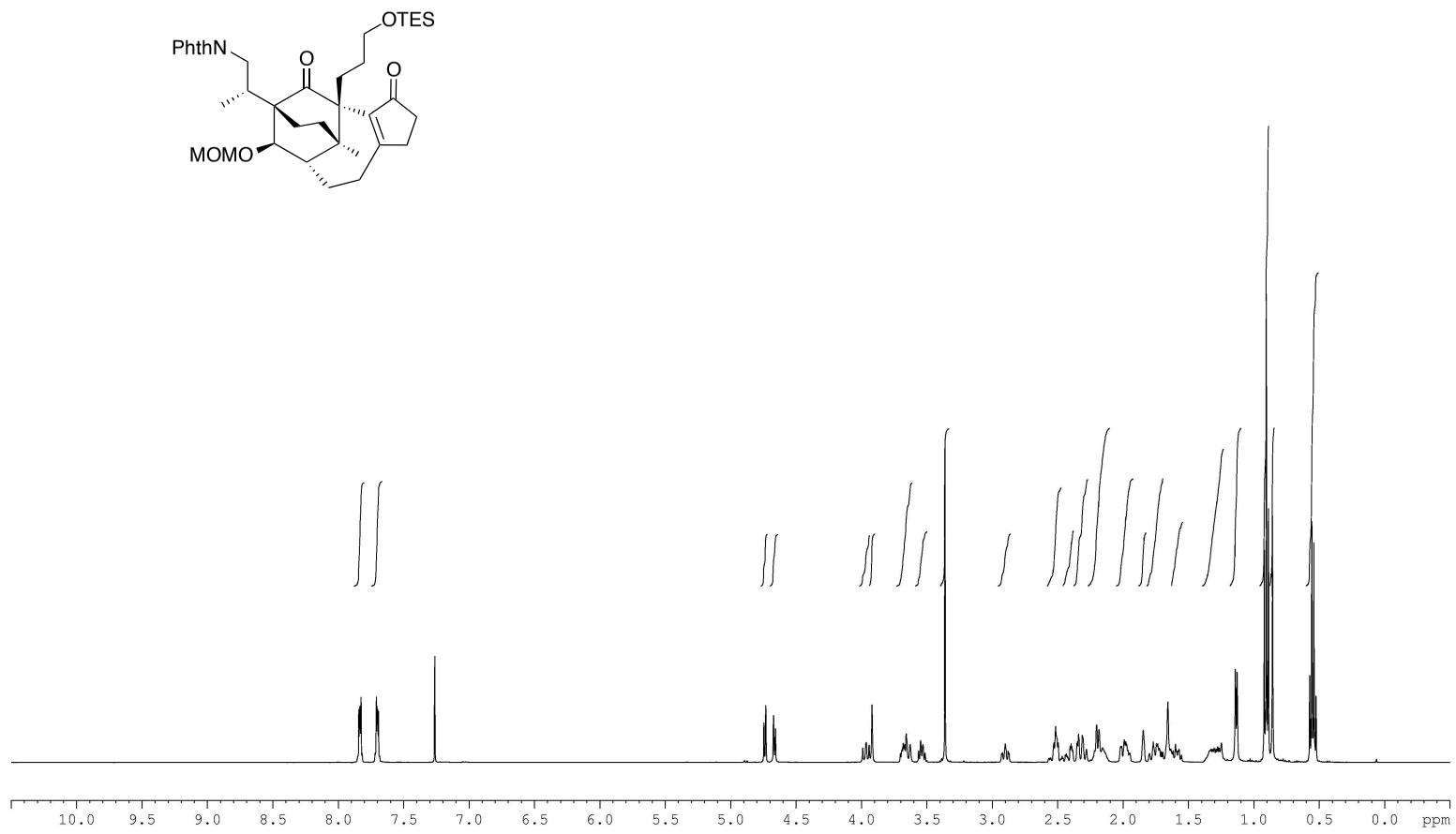



**Figure A3-25:** The 500 MHz $^{1}$H NMR Spectrum of Comopund (+)-**4.10** in $CDCl_3$

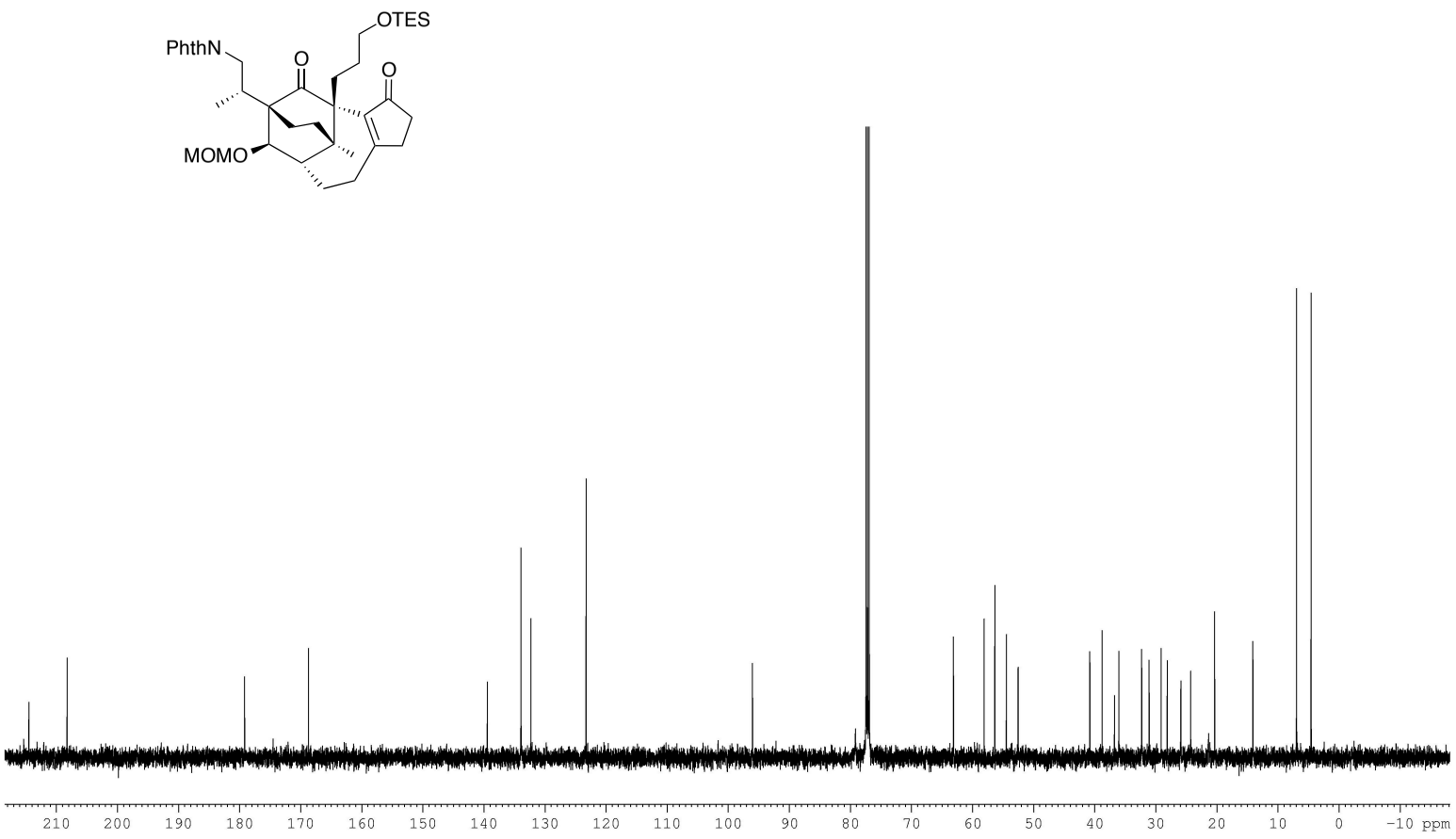



**Figure A3-26:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**4.10** in $CDCl_3$

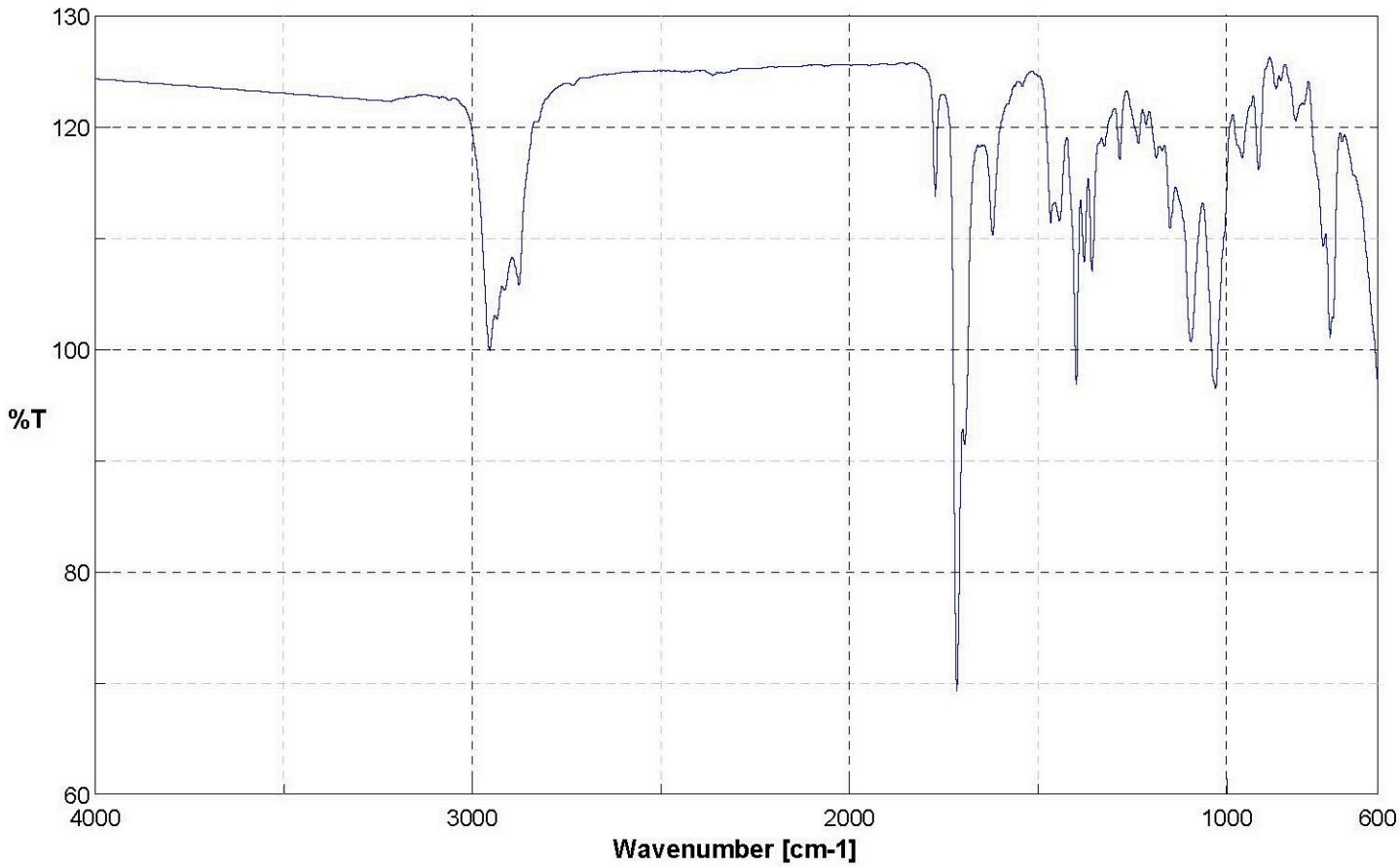



**Figure A3-27:** The Infrared Spectrum of Compound (+)-**4.10**

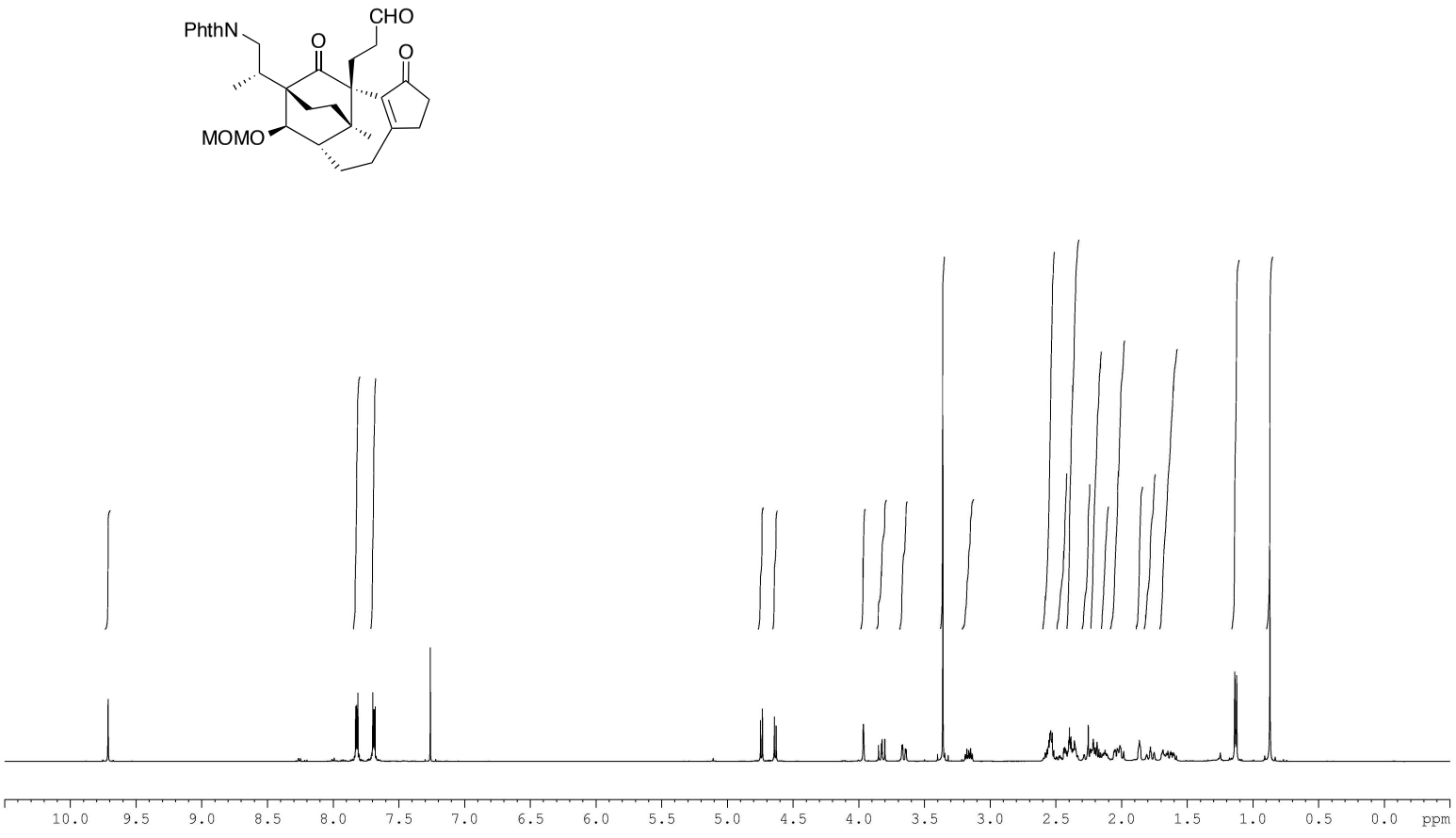



**Figure A3-28:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**4.11** in $CDCl_3$

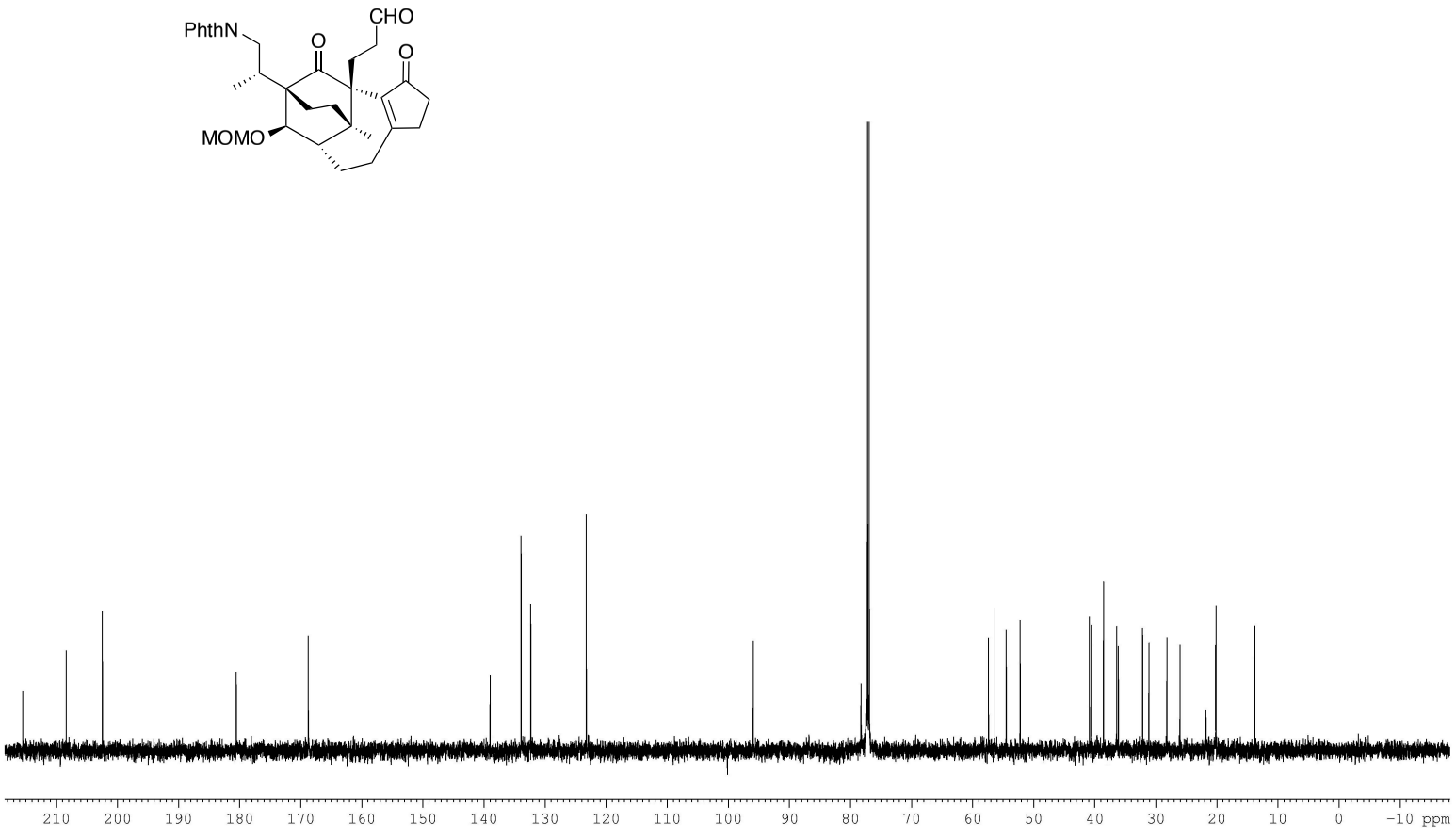



**Figure A3-29:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**4.11** in $CDCl_3$

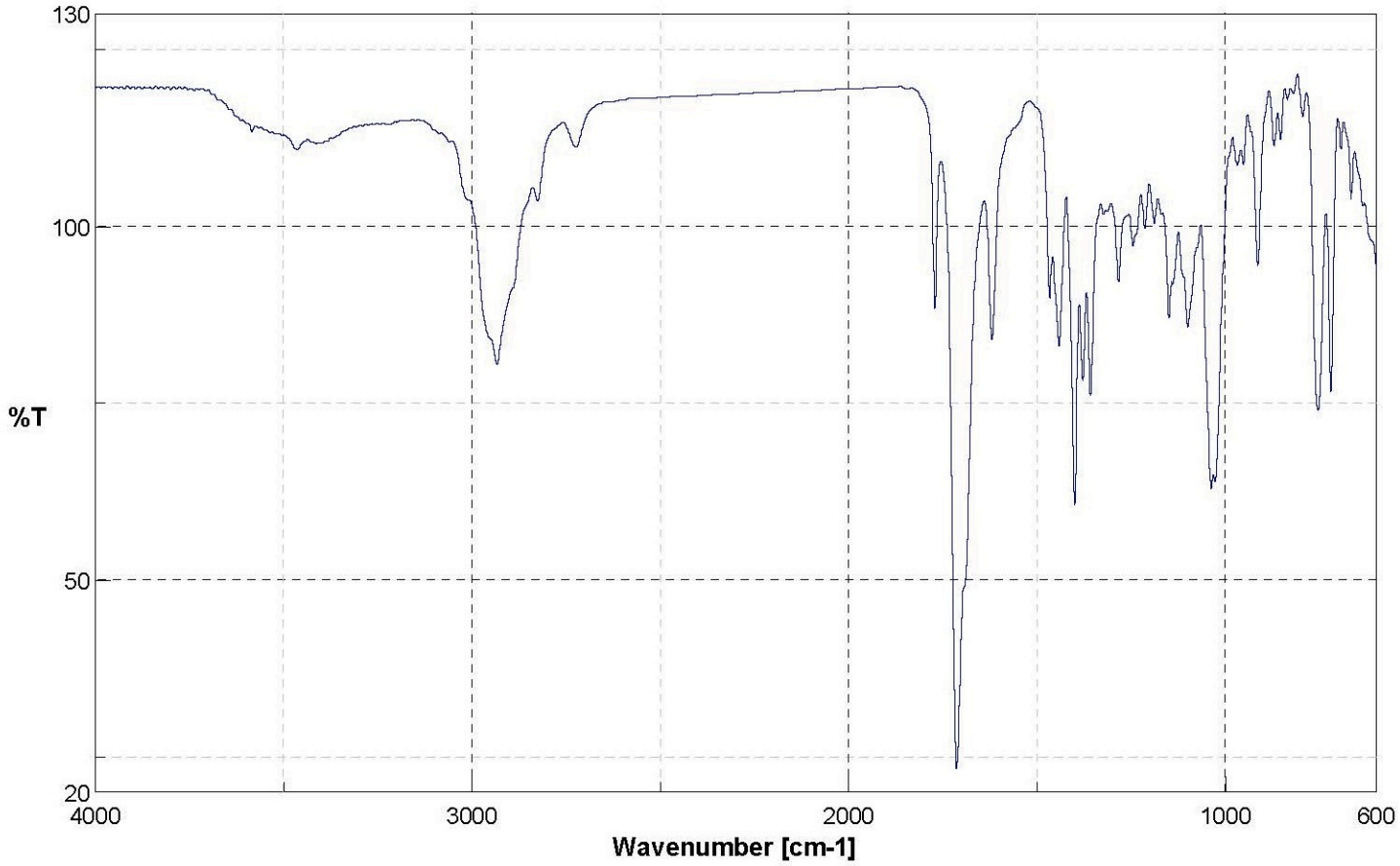



**Figure A3-30:** The Infrared Spectrum of Compound (+)-**4.11**

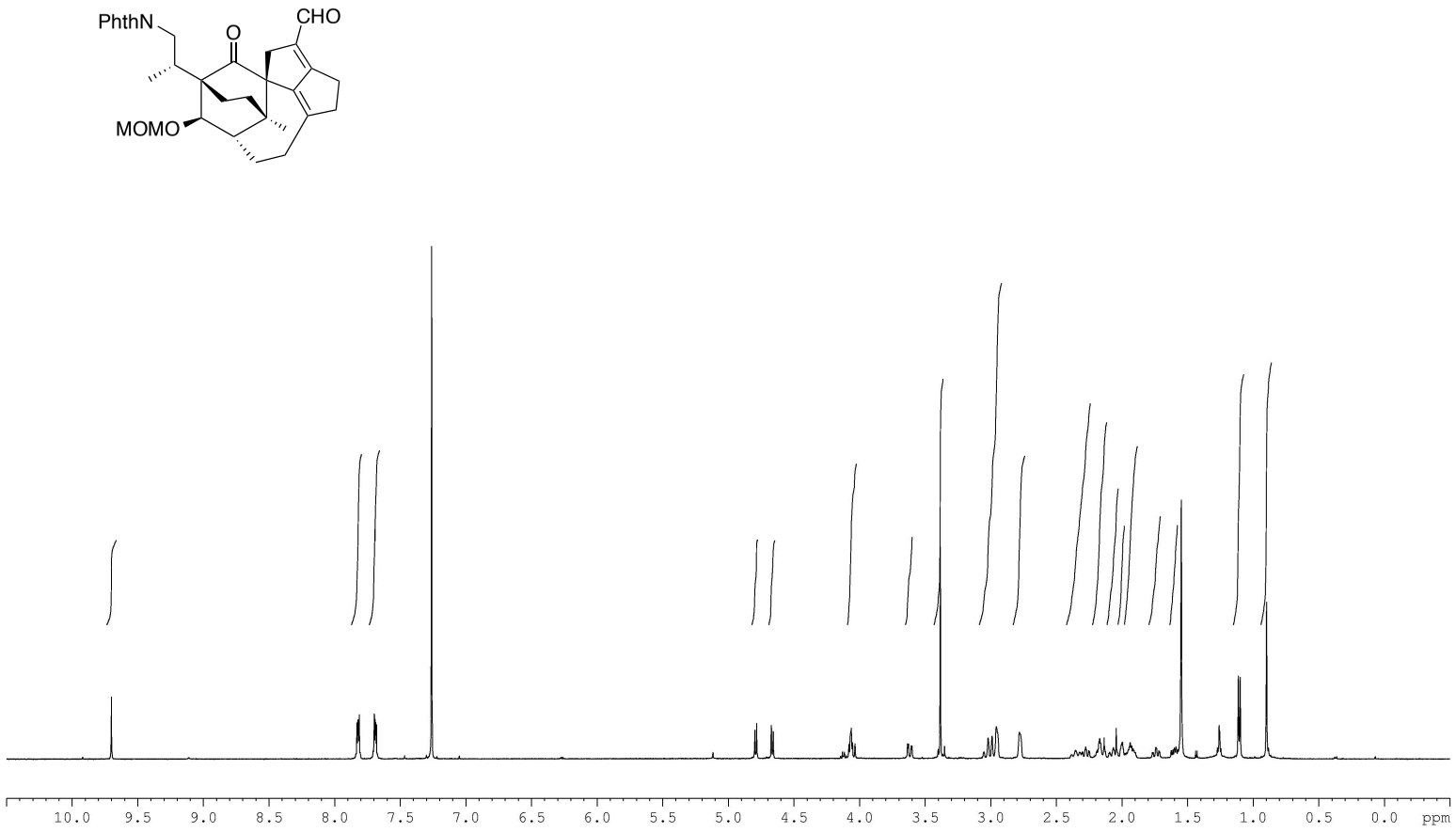



**Figure A3-31:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**4.12** in $CDCl_3$

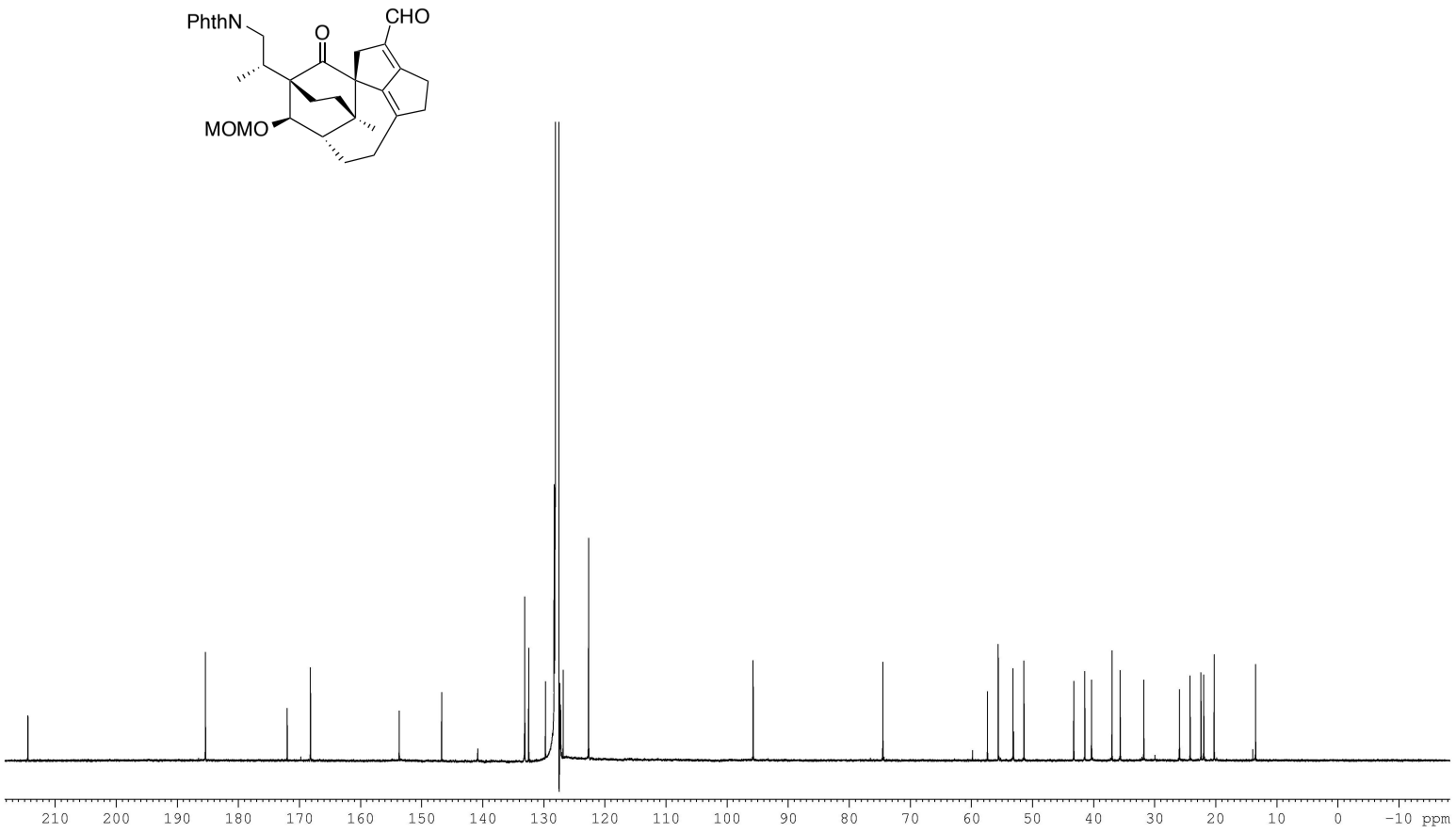



**Figure A3-32:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**4.12** in $C_6D_6$

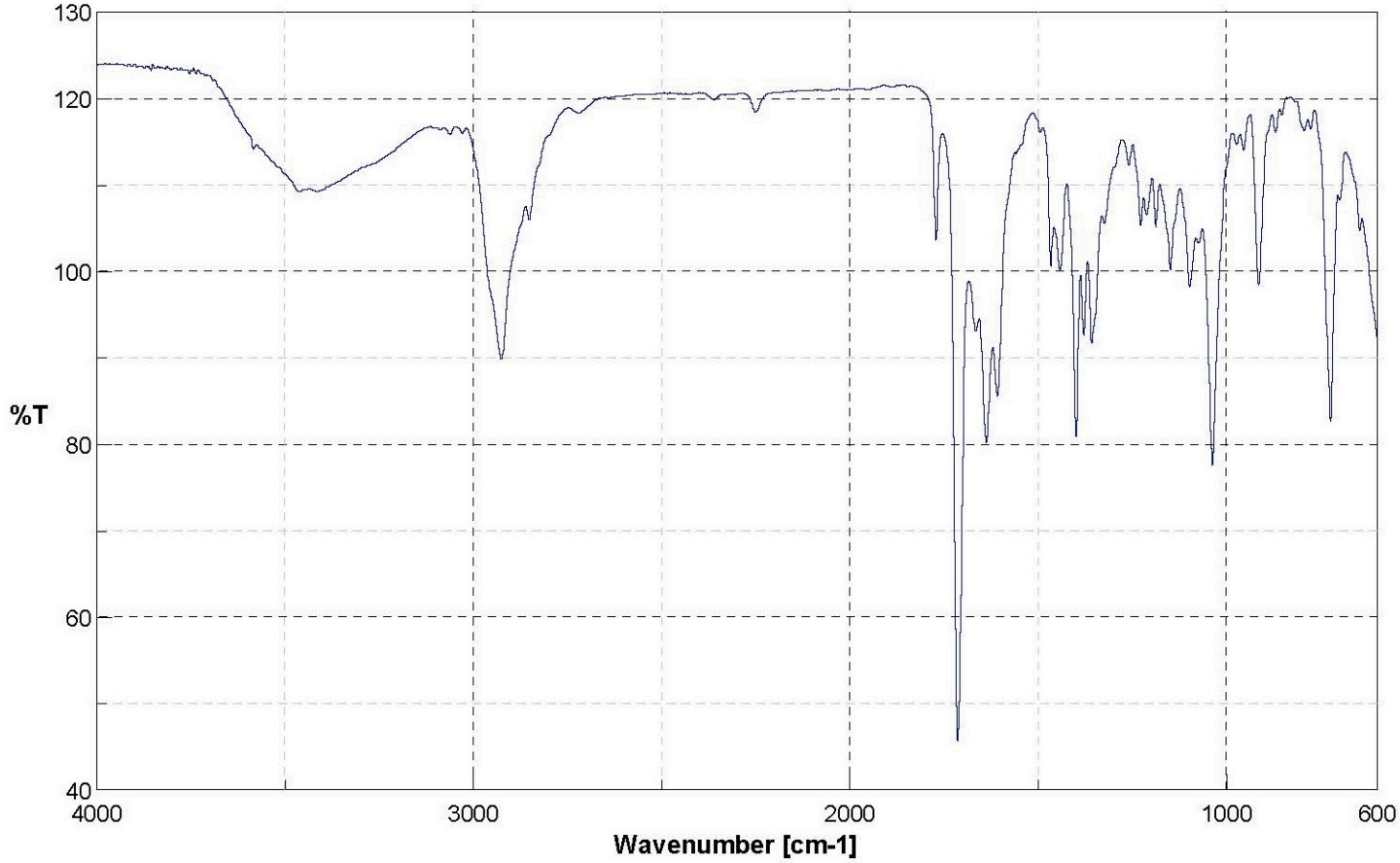



**Figure A3-33:** The Infrared Spectrum of Compound (+)-**4.12**

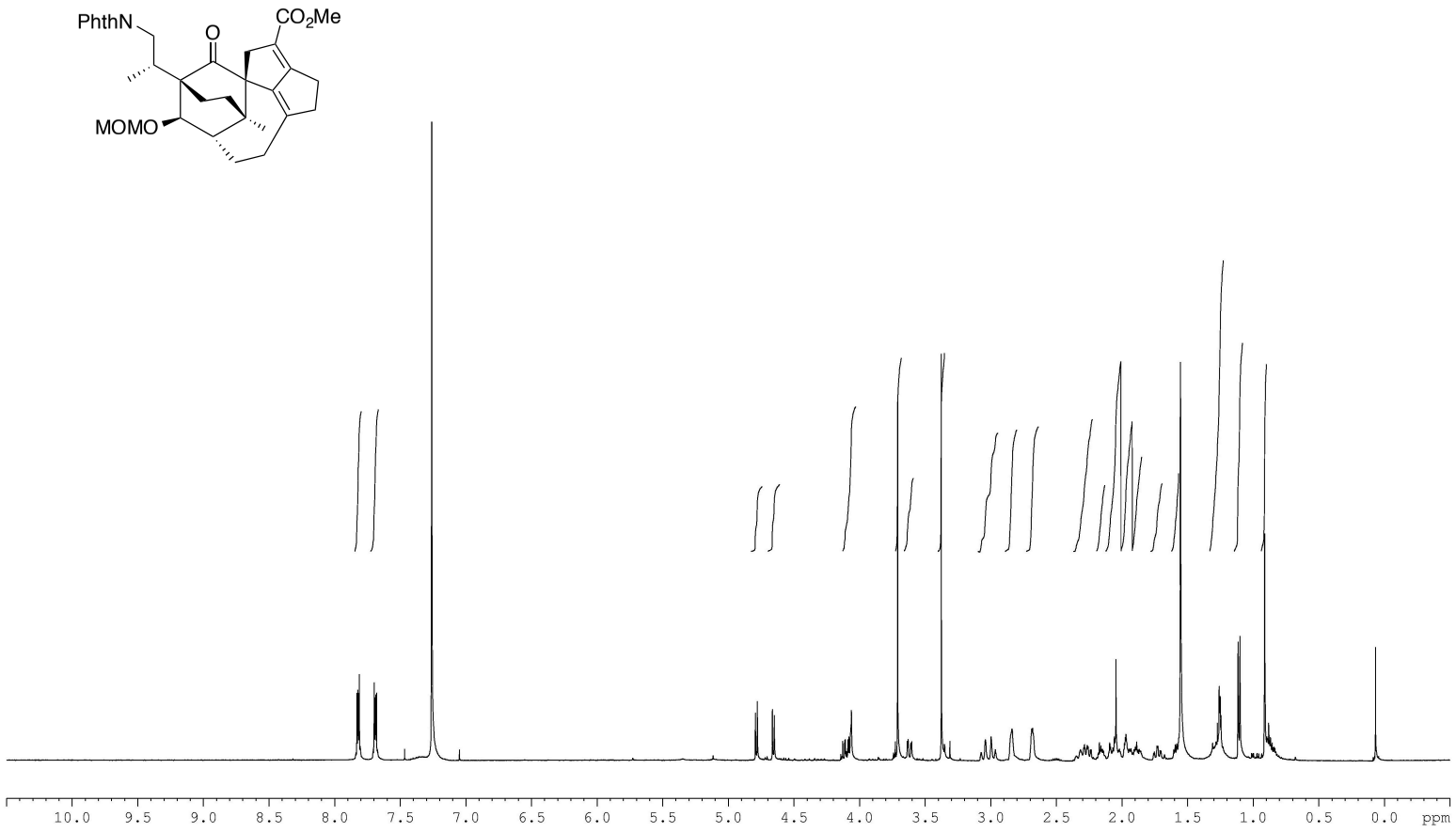



**Figure A3-34:** The 500 MHz $^{1}$H NMR Spectrum of Compound (+)-**4.14** in $CDCl_3$

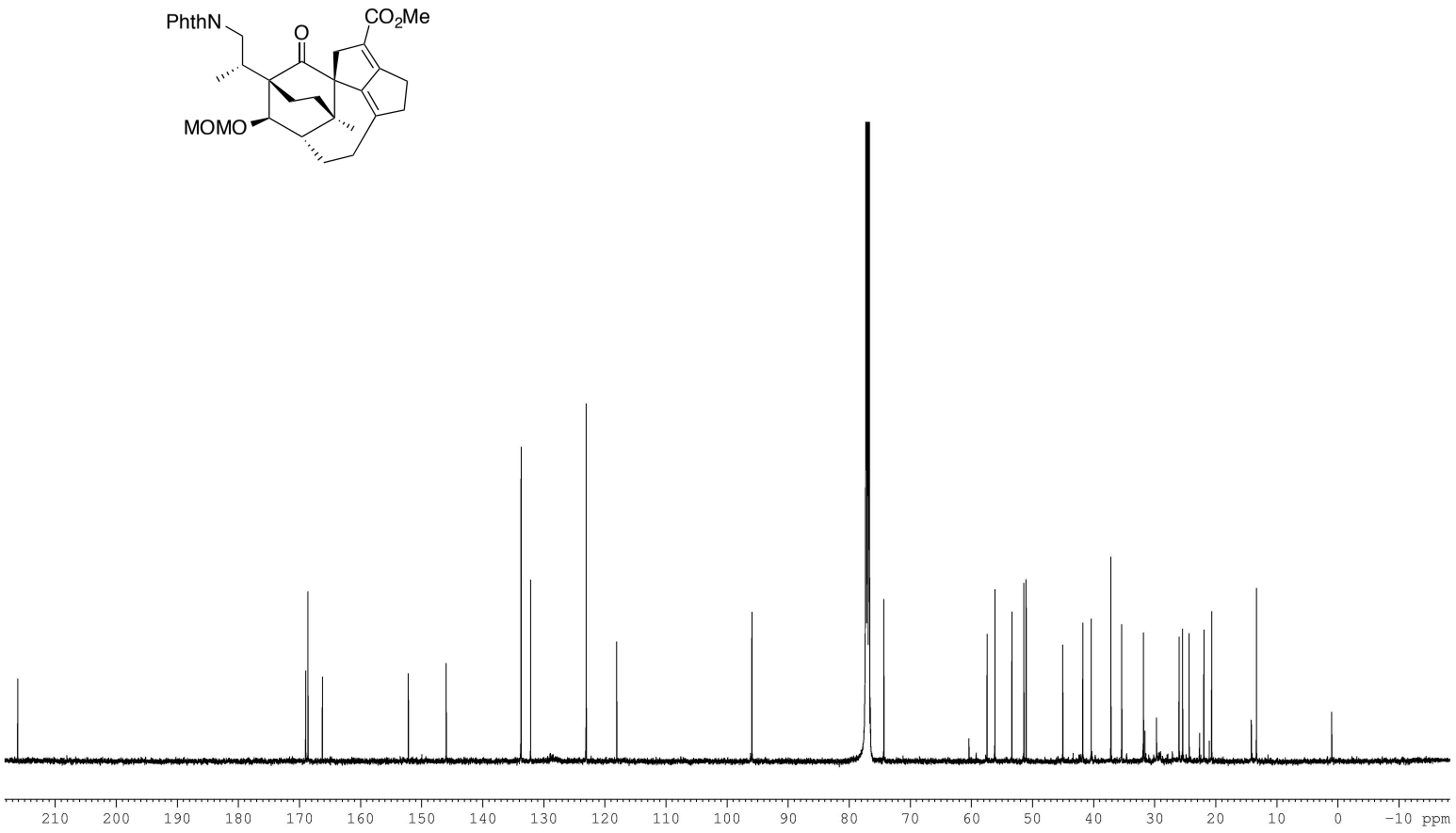



**Figure A3-35:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (+)-**4.14** in $CDCl_3$

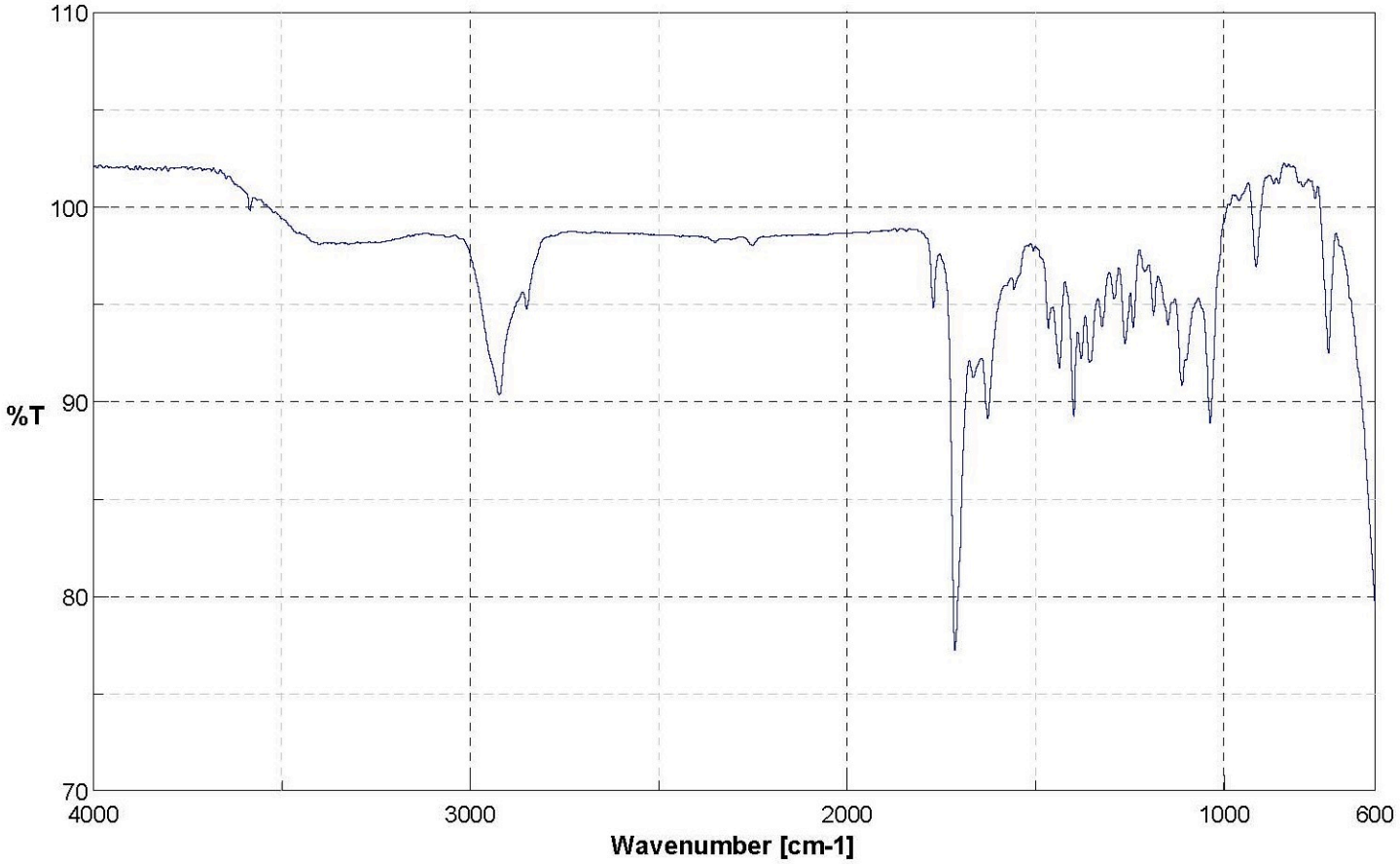



**Figure A3-36:** The Infrared Spectrum of Compound (+)-**4.14**

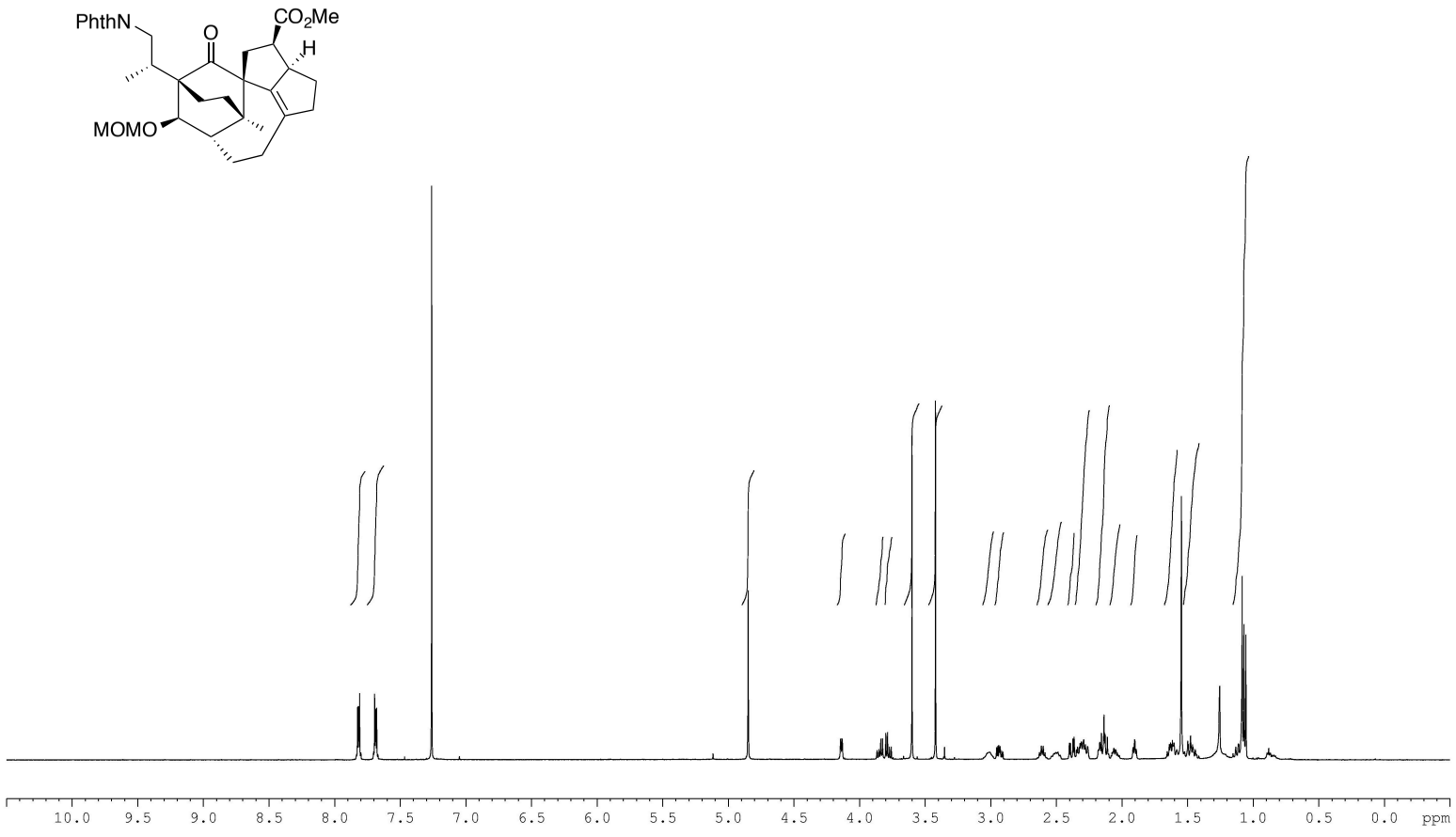



**Figure A3-37:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**4.15** in $CDCl_3$

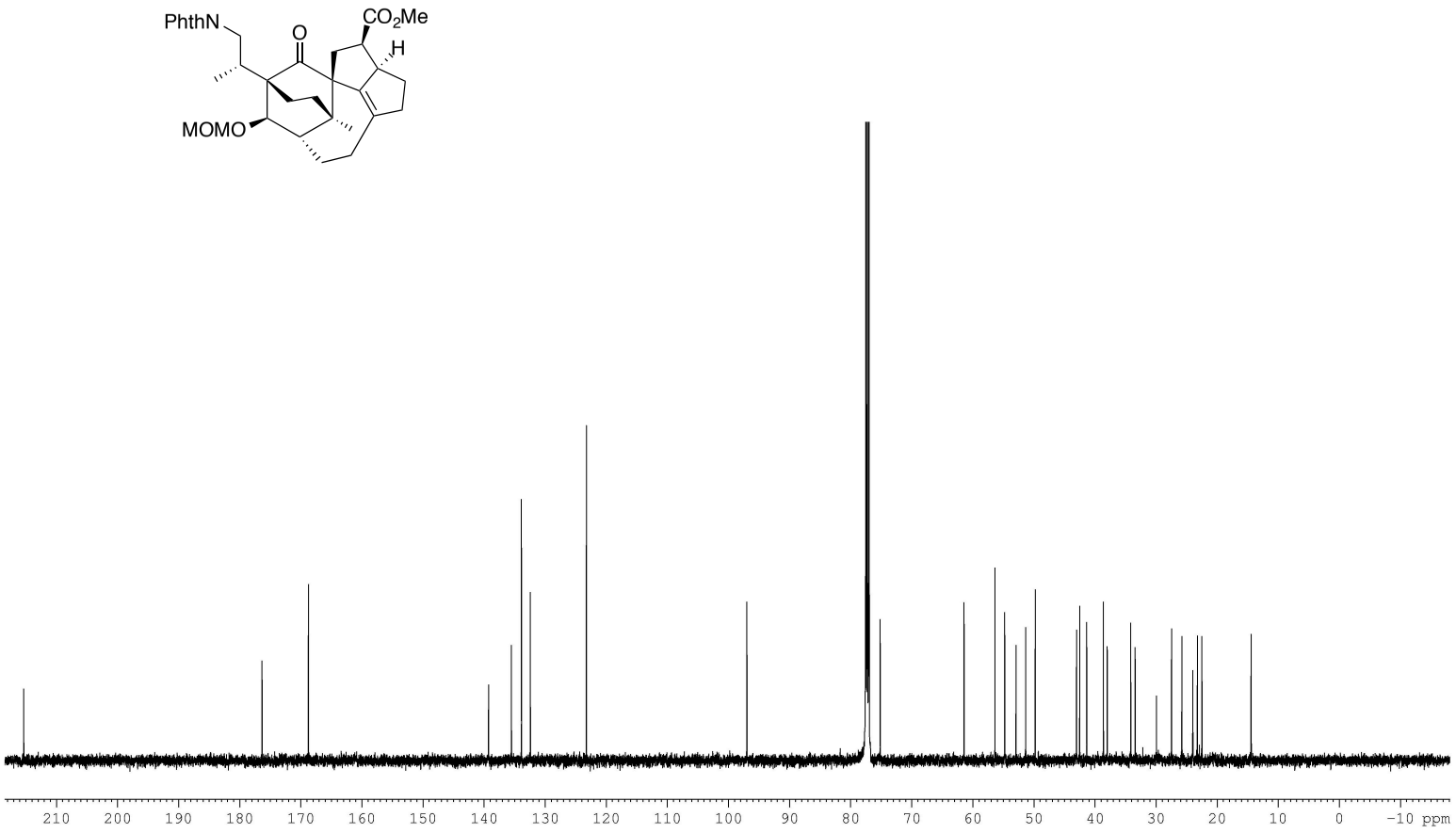



**Figure A3-38:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**4.15** in $CDCl_3$

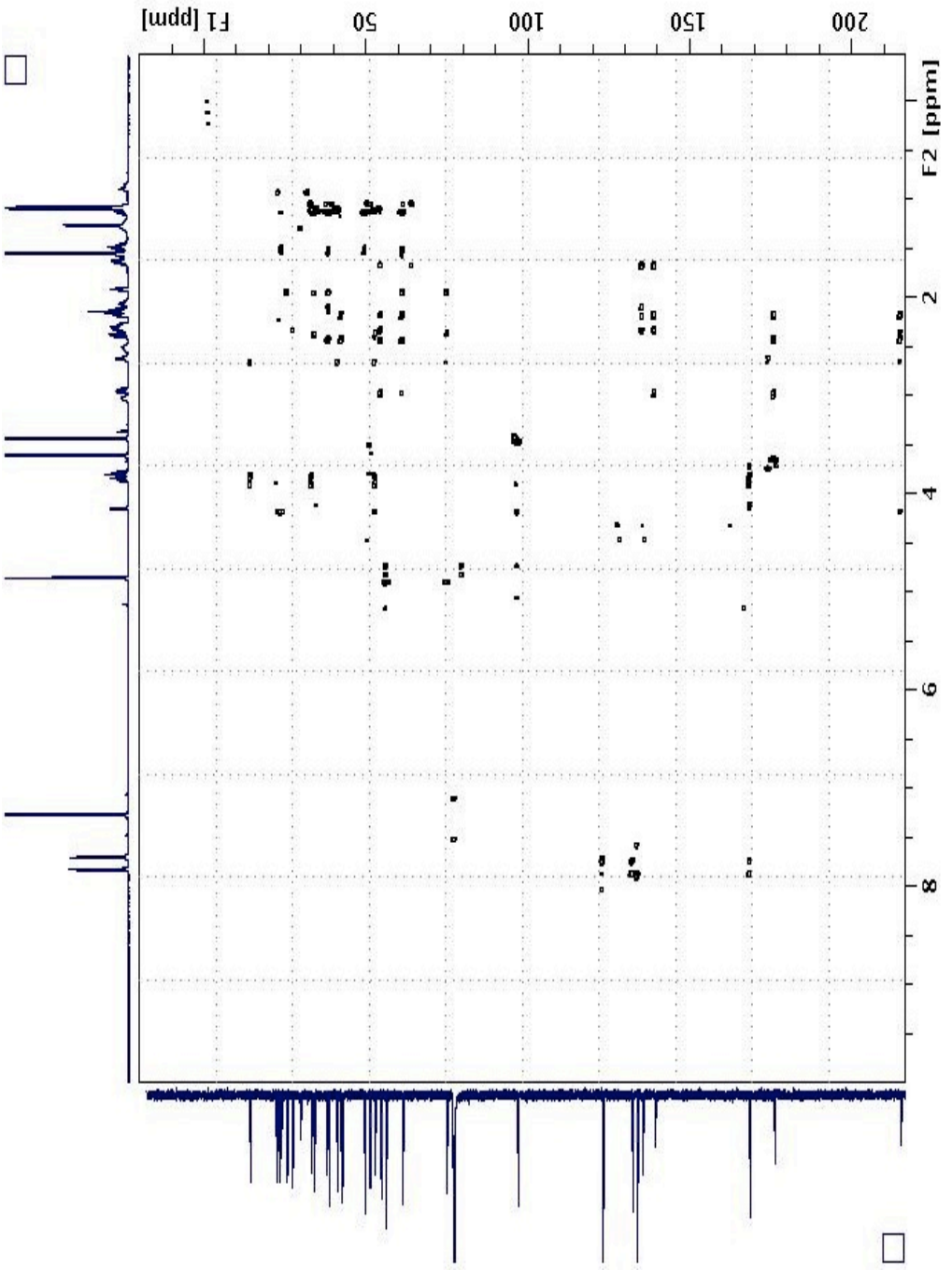



**Figure A3-39:** The HMBC Spectrum of Compound (–)-**4.15** in $CDCl_3$

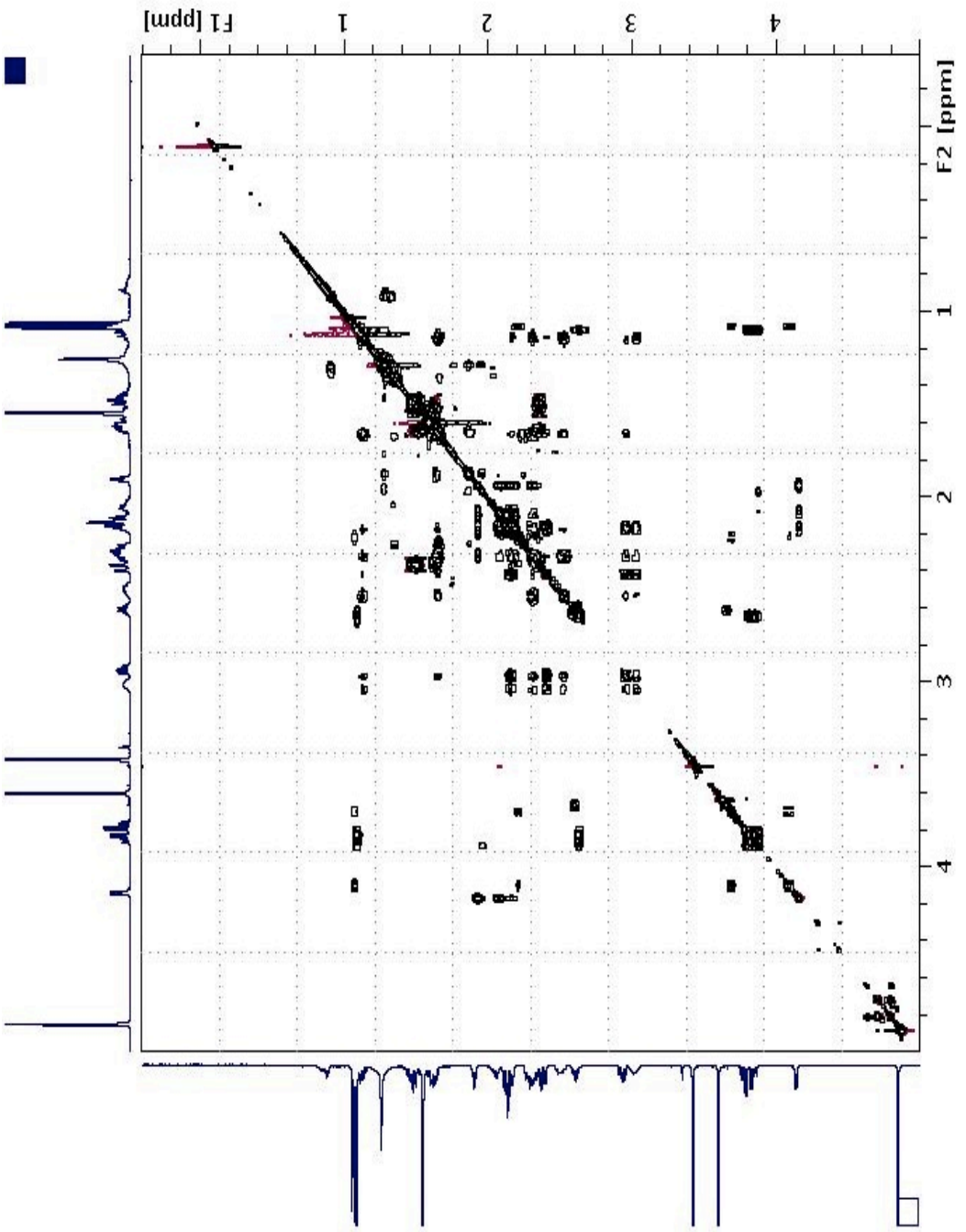



**Figure A3-40:** The TOCSY Spectrum of Compound (–)-**4.15** in $CDCl_3$

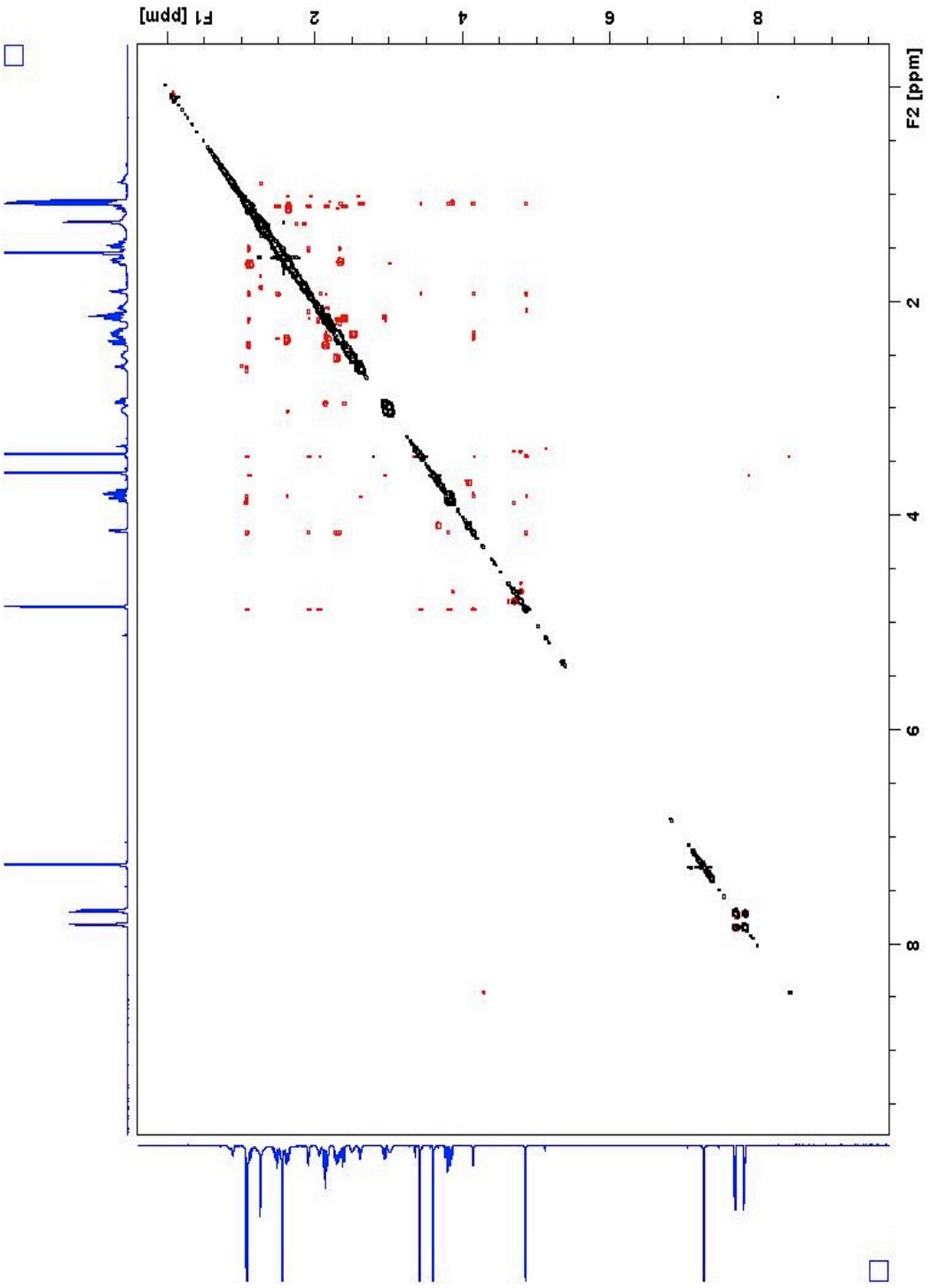



**Figure A3-41:** The NOESY Spectrum of Compound (–)-**4.15** in $CDCl_3$

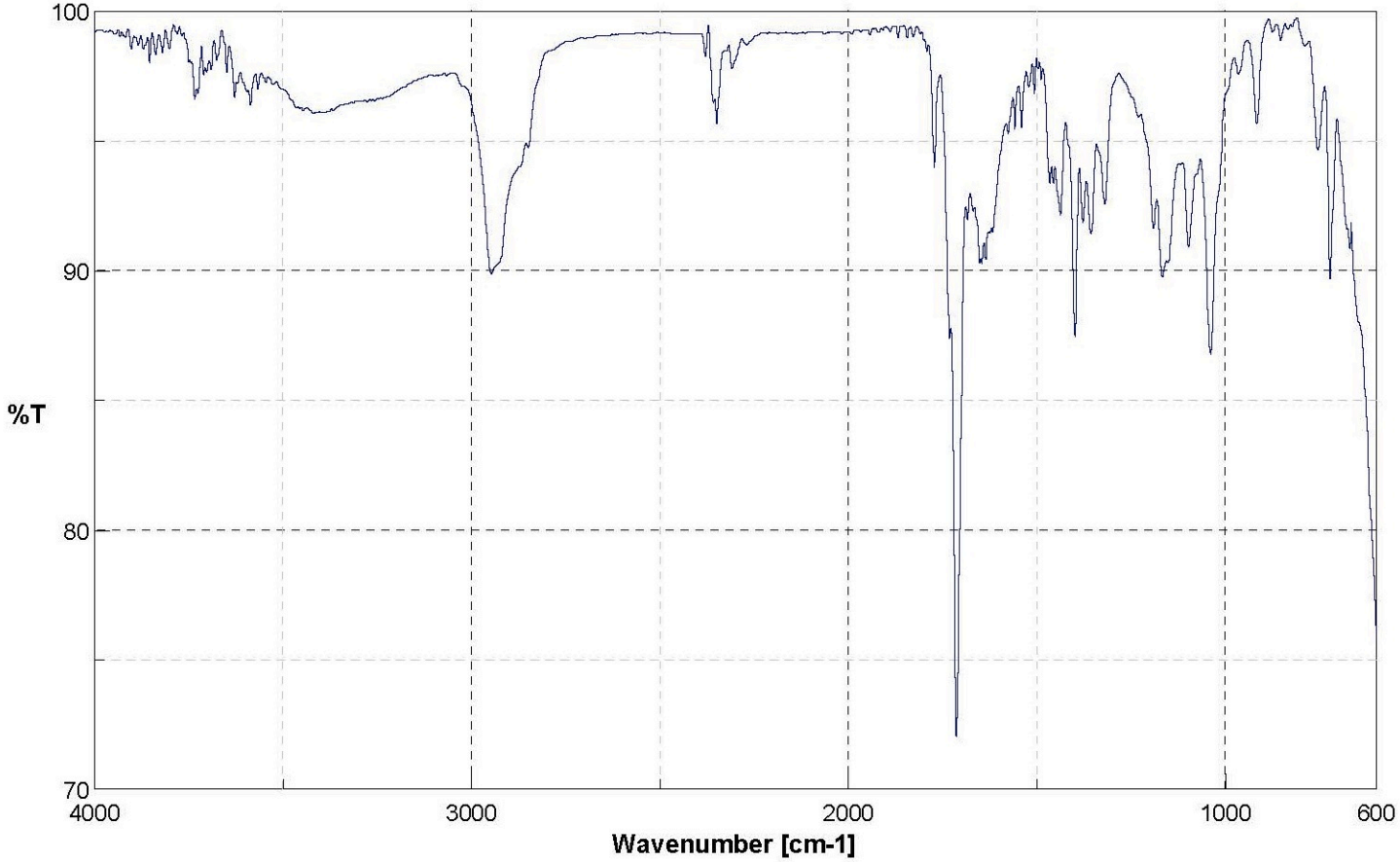



**Figure A3-42:** The Infrared Spectrum of Compound (–)-**4.15**

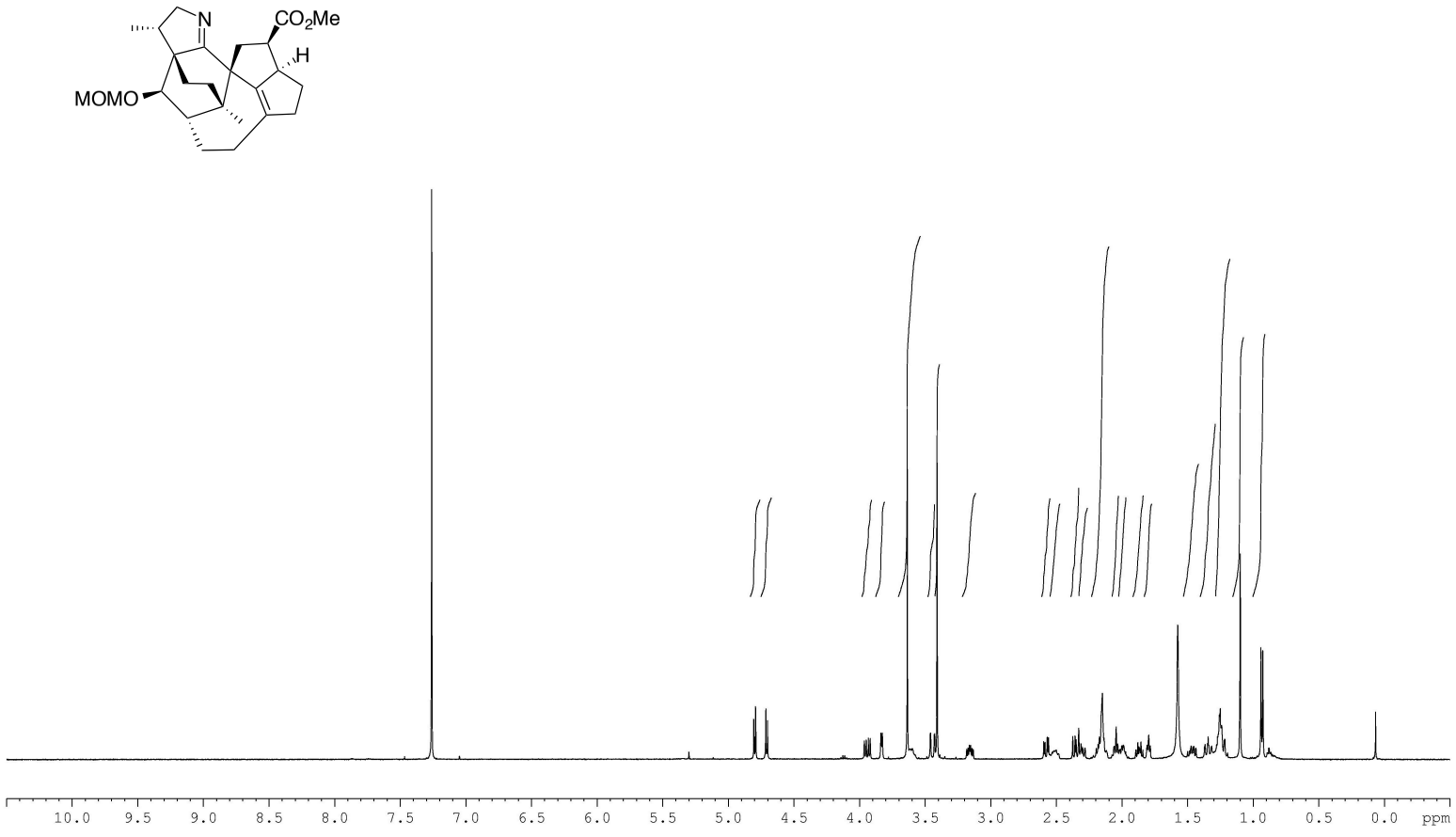



**Figure A3-43:** The 500 MHz $^{1}$H NMR Spectrum of Compound (–)-**4.16** in $CDCl_3$

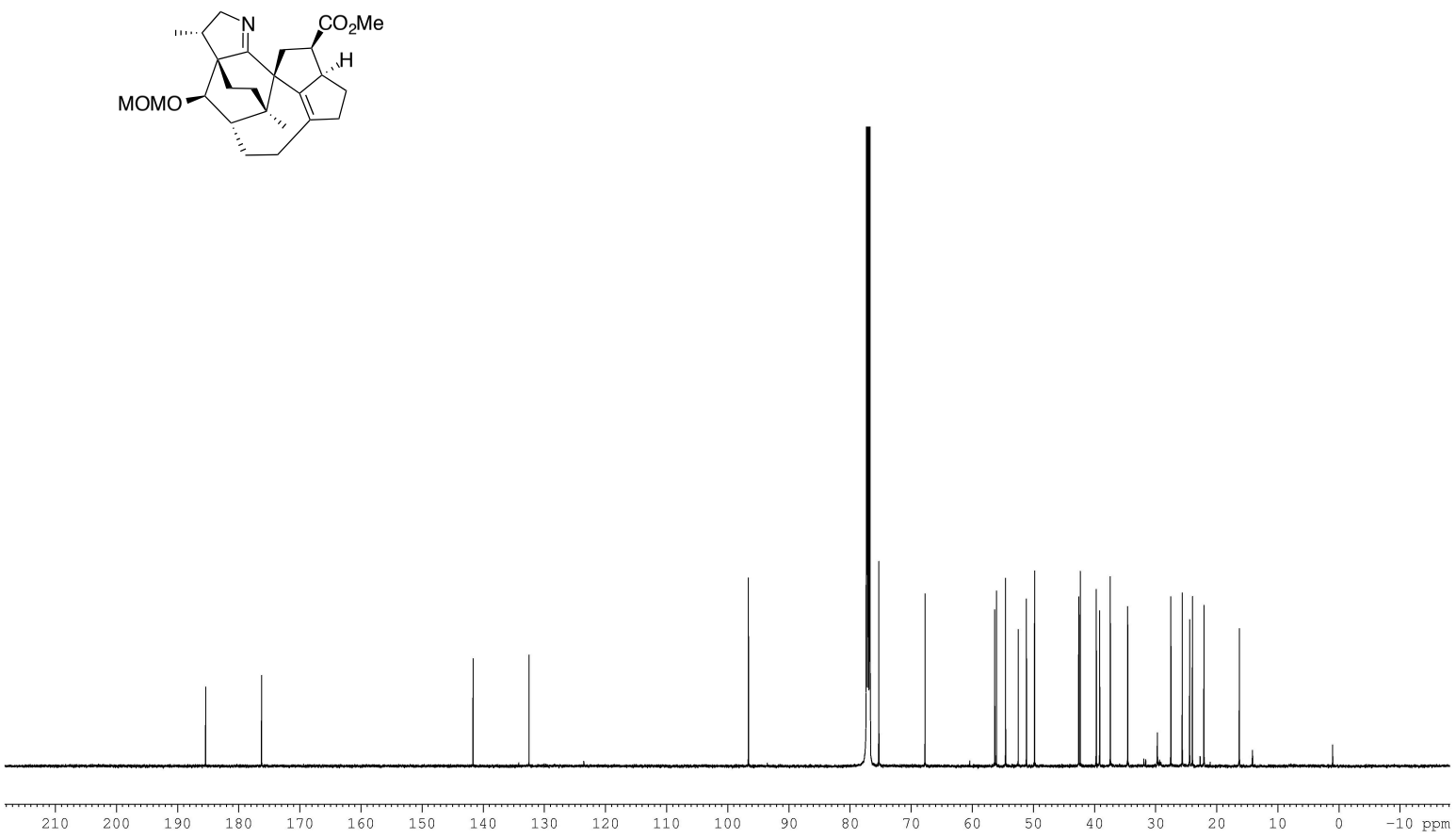



**Figure A3-44:** The 125 MHz $^{13}C$ NMR Spectrum of Compound (–)-**4.16** in $CDCl_3$

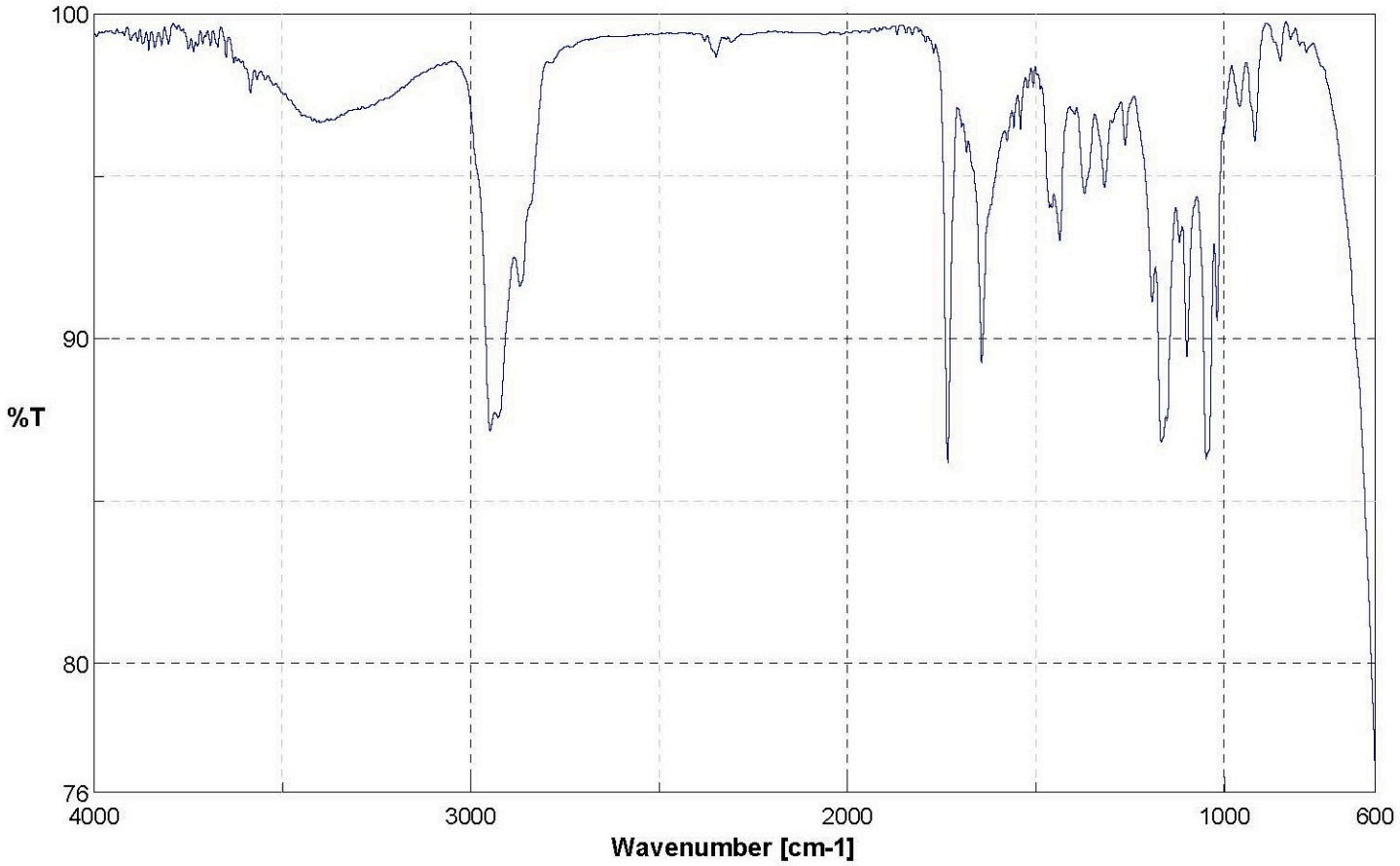



**Figure A3-45:** The Infrared Spectrum of Compound (–)-**4.16**

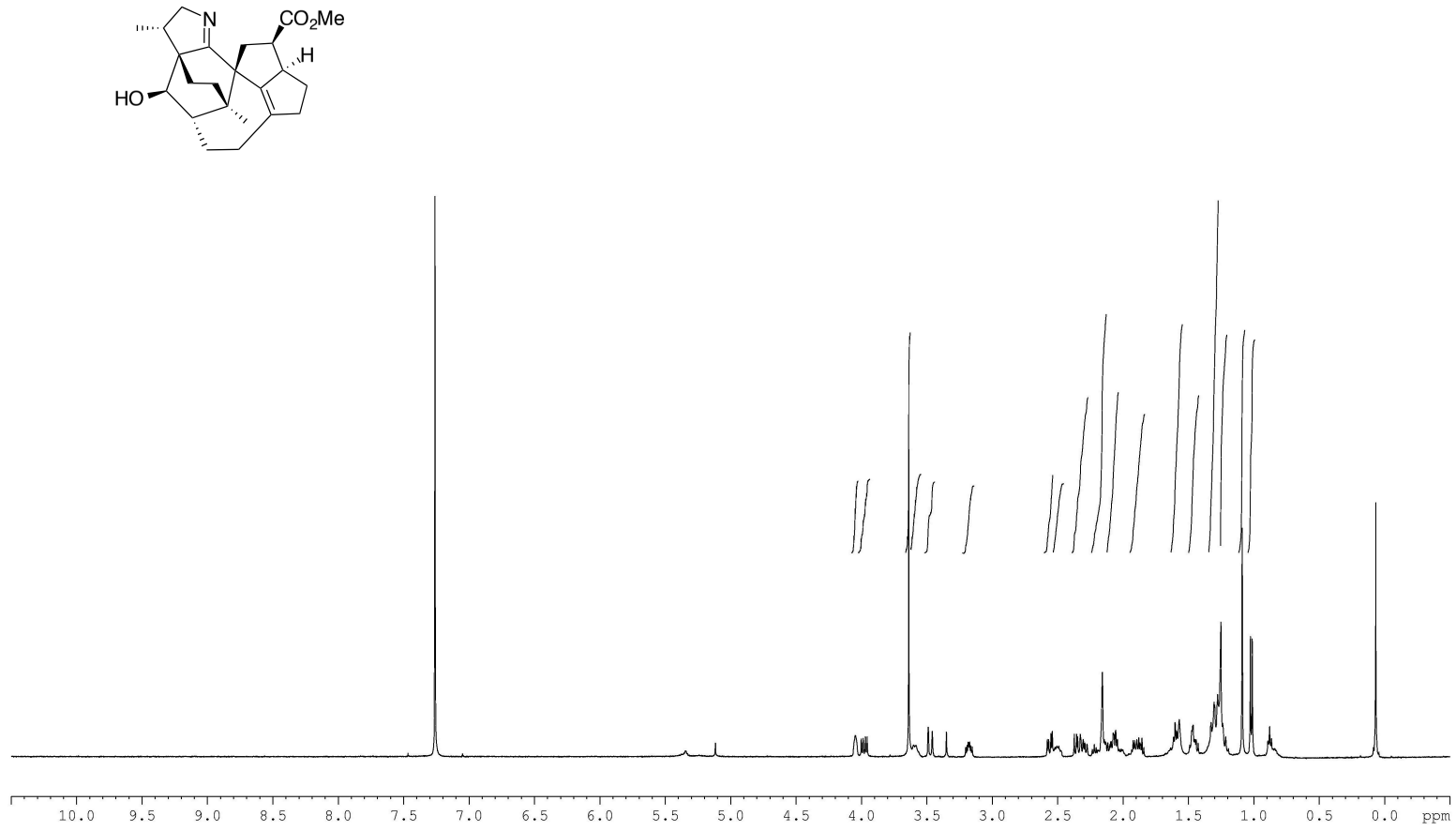



**Figure A3-46:** The 500 MHz $^{1}$H NMR Spectrum of (–)-Calyciphylline N (**1.15**) in $CDCl_3$

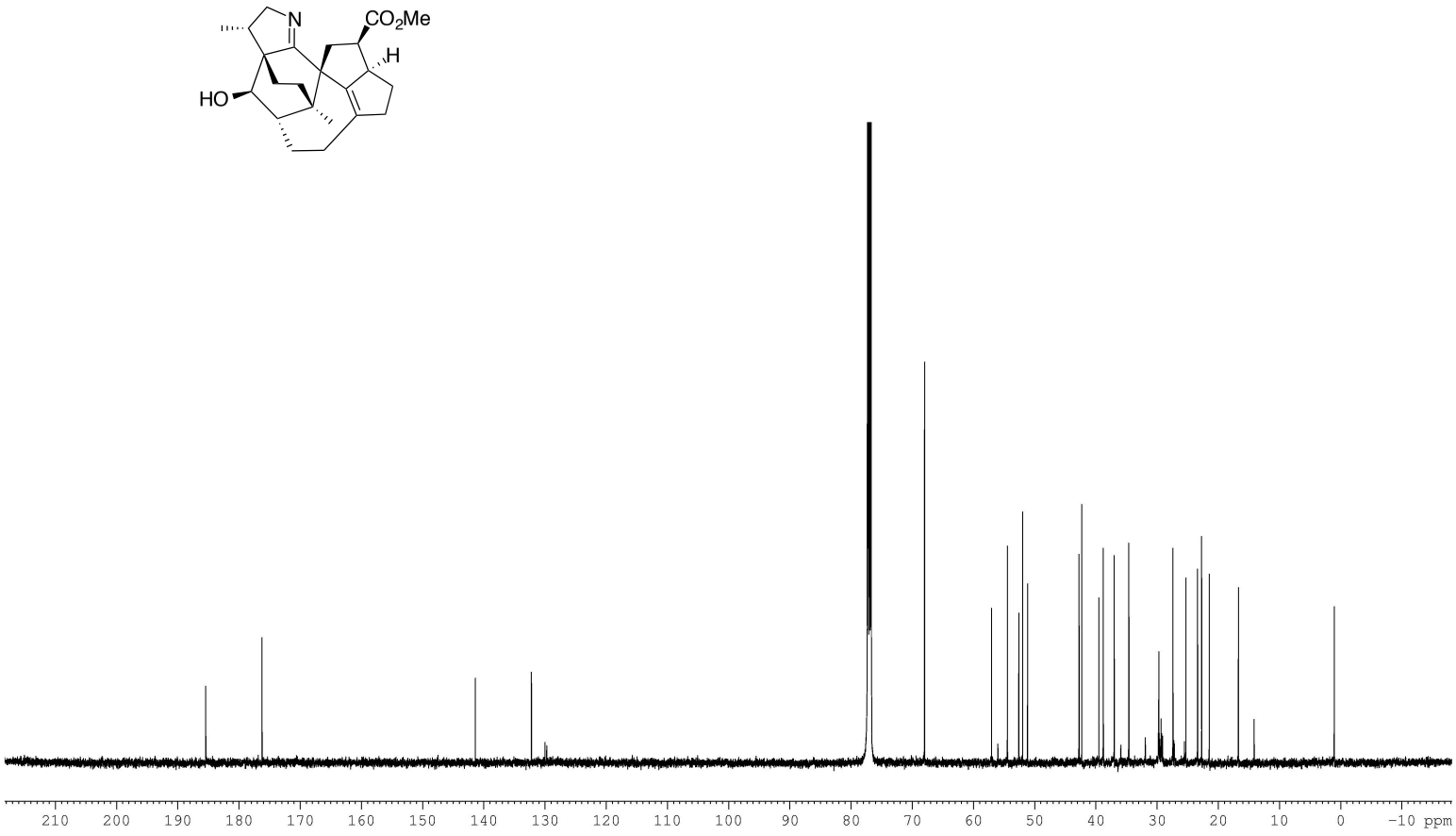



**Figure A3-47:** The 125 MHz $^{13}C$ NMR Spectrum of (–)-Calyciphylline N (**1.15**) in $CDCl_3$

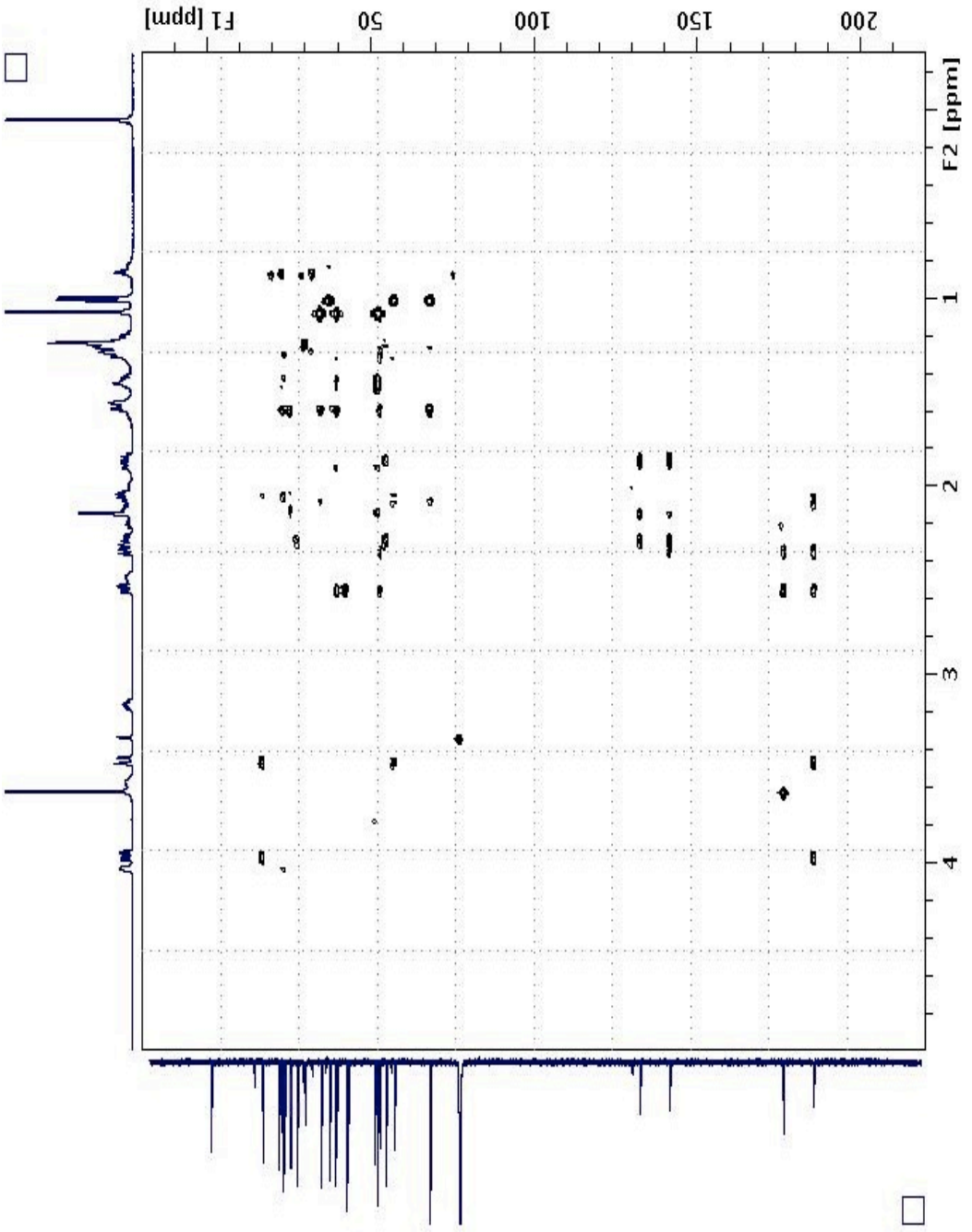



**Figure A3-48:** The HMBC Spectrum of (–)-Calyciphylline N (**1.15**) in $CDCl_3$

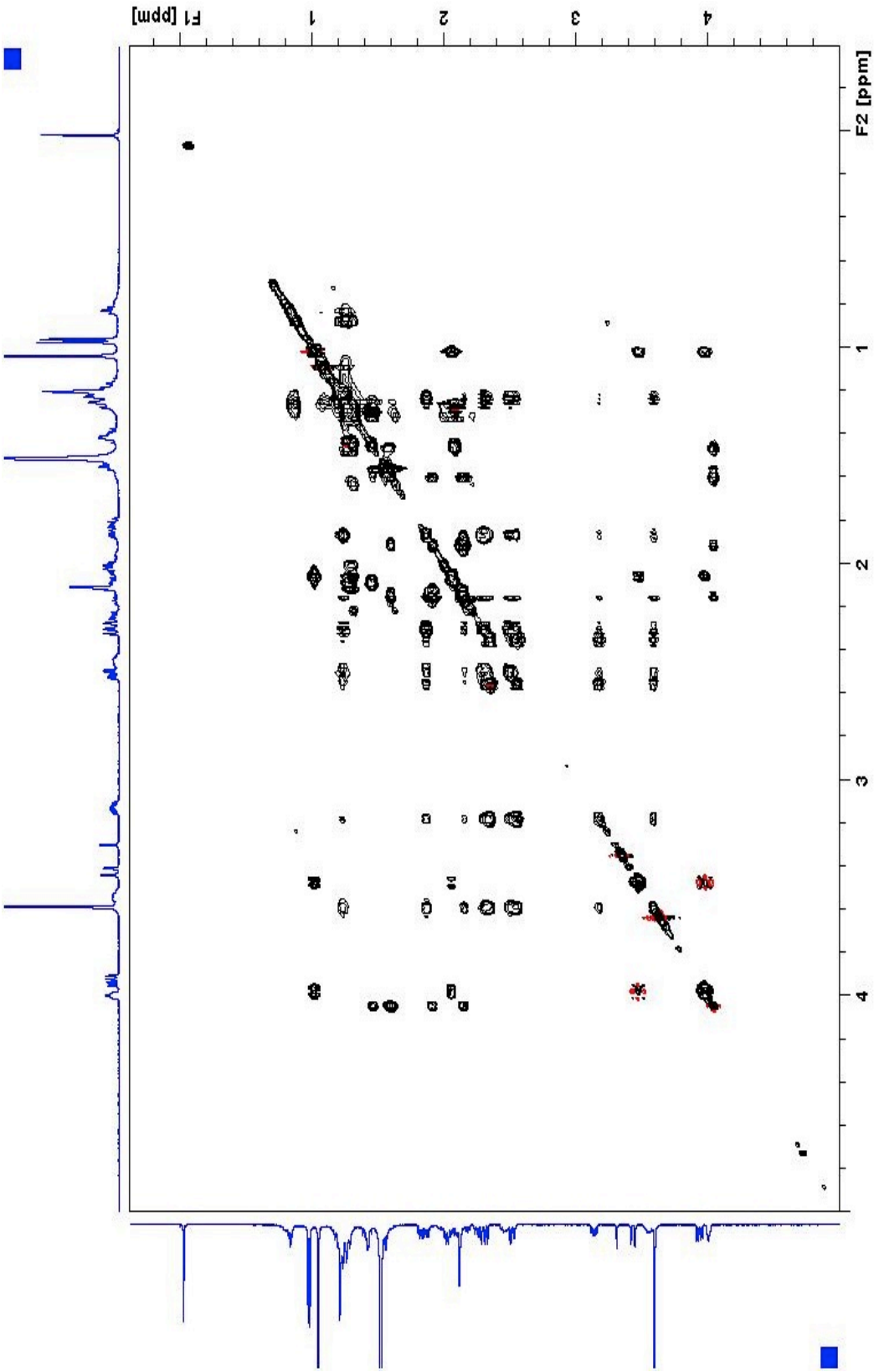



**Figure A3-49:** The TOCSY Spectrum of (–)-Calyciphylline N **(1.15)** in $CDCl_3$

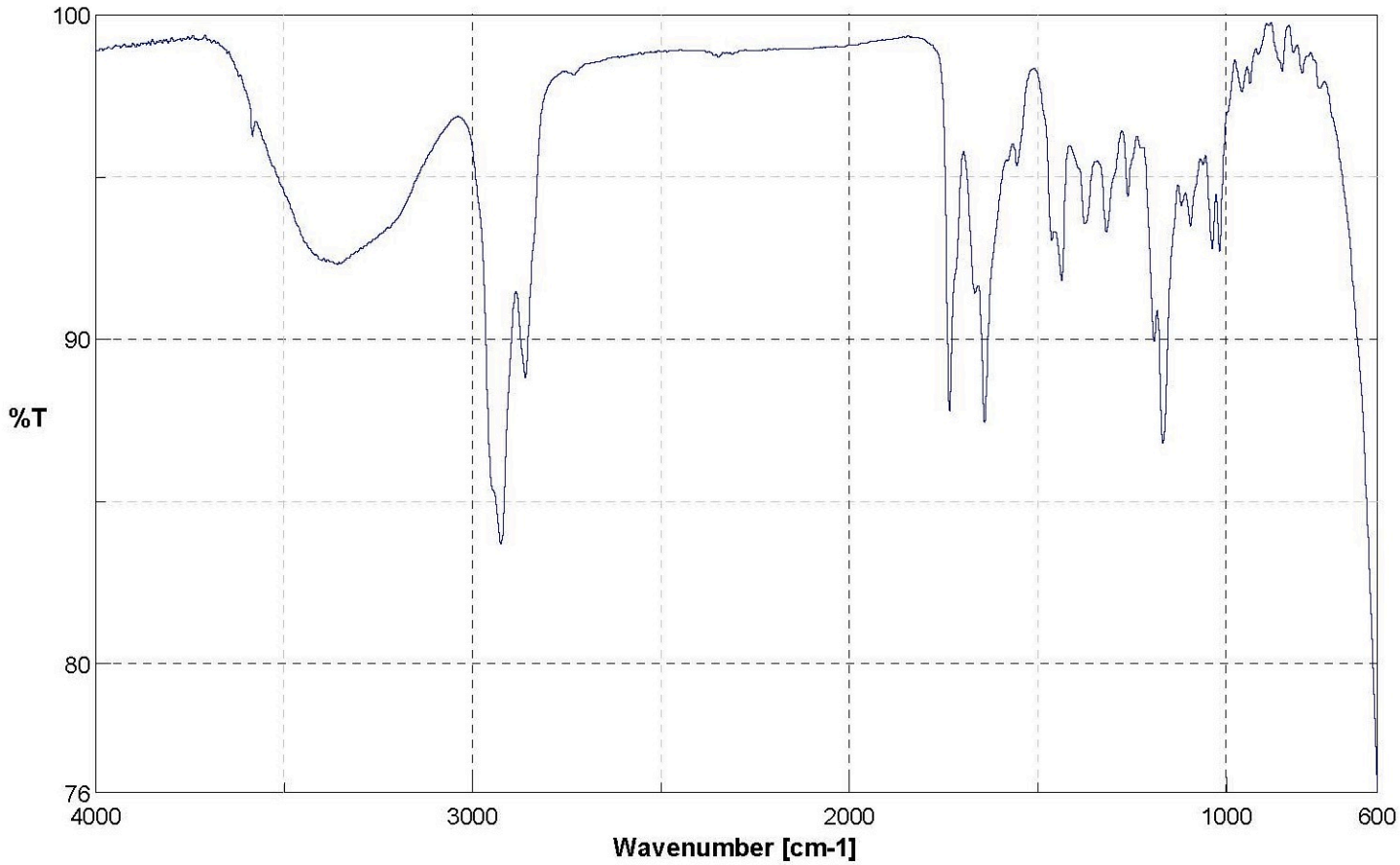
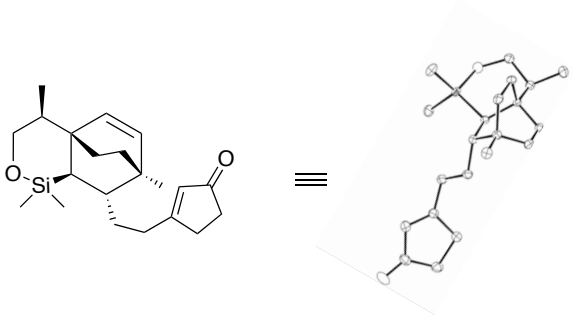



**Figure A3-50:** The Infrared Spectrum of (–)-Calyciphylline N (**1.15**)

# Appendix 4: X-Ray Crystallographic Data for Compound (–)-2.20

## X-Ray Structure Determination of Compound (–)-2.20



Compound (–)-**2.20**, $C_{21}H_{32}SiO_2$, crystallizes in the orthorhombic space group $P2_12_12_1$ (systematic absences h00: h=odd, 0k0: k=odd, and 00l: l=odd) with a=6.3483(4)Å, b=8.5872(5)Å, c=35.965(2)Å, V=1960.6(2)Å$^3$, Z=4, and $d_{calc}$=1.167 g/cm$^3$ . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-K$\alpha$ radiation ($\lambda$=0.71073 Å) at a temperature of 143(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 5 seconds. A total of 1118 frames were collected with a crystal to detector distance of 38.276 mm, rotation widths of 0.5° and exposures of 5 seconds:

| scan type | 2θ | ω | ϕ | χ | frames |
|---|---|---|---|---|---|
| ϕ | 19.50 | 59.55 | -11.29 | -26.26 | 739 |
| ω | -20.50 | -18.67 | -181.36 | -31.86 | 73 |
| ω | 17.00 | -35.92 | -175.56 | 82.07 | 110 |
| ω | -15.50 | -109.19 | 18.69 | 41.79 | 196 |

Rotation frames were integrated using SAINT, producing a listing of unaveraged $F^2$ and $\sigma(F^2)$ values which were then passed to the SHELXTL program package for further processing and structure solution. A total of 19057 reflections were measured over the ranges $2.44 \leq \theta \leq 25.04°$, $-7 \leq h \leq 7$, $-10 \leq k \leq 10$, $-42 \leq l \leq 42$ yielding 3465 unique reflections (Rint = 0.0282). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS (minimum and maximum transmission 0.6705, 0.7452).

The structure was solved by direct methods (SHELXS-97). Refinement was by full-matrix least squares based on $F^2$ using SHELXL-97. All reflections were used during refinement. The

weighting scheme used was $w=1/[\sigma^2(F_o^2)+ (0.0390P)^2 + 0.5007P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.0303 and wR2=0.0768 for 3382 observed reflections for which $F > 4\sigma(F)$ and R1=0.0312 and wR2=0.0777 and GOF =1.081 for all 3465 unique, non-zero reflections and 222 variables. The maximum $\Delta/\sigma$ in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were +0.252 and -0.168 e/Å$^3$.

Table A4.1 lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables A3.2 and A3.3. Anisotropic thermal parameters are in Table A3.4. Tables A4.5 and A4.6 list bond distances and bond angles. Figure 5.1 is an ORTEP representation of the molecule with 30% probability thermal ellipsoids displayed.

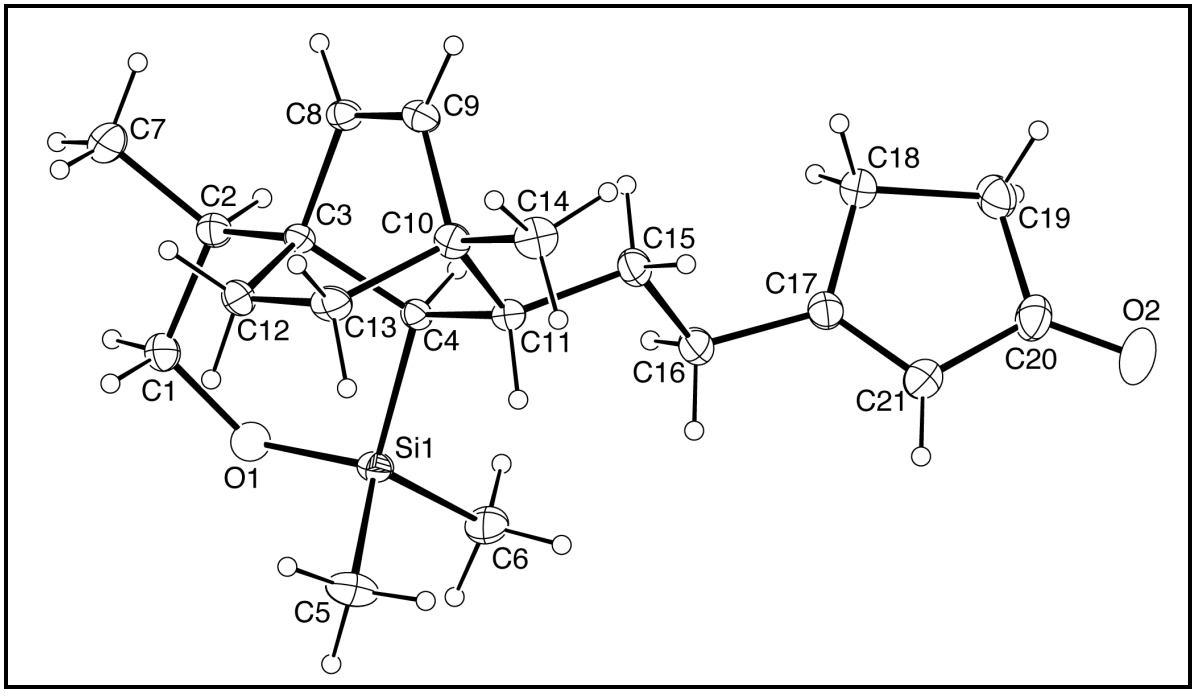



**Figure A4.1:** ORTEP drawing of compound (–)-**2.20** with 30% probability thermal ellipsoids.

**Table A4.1:** Summary of Structure Determination of Compound (–)-**2.20**

| | |
|---|---|
| Empirical formula | $C_{21}H_{32}SiO_2$ |
| Formula weight | 344.56 |
| Temperature | 143(1) K |
| Wavelength | 0.71073 Å |
| Crystal system | orthorhombic |
| Space group | $P2_12_12_1$ |
| Cell constants: | |
| a | 6.3483(4) Å |
| b | 8.5872(5) Å |
| c | 35.965(2) Å |
| Volume | 1960.6(2) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.167 $Mg/m^3$ |
| Absorption coefficient | 0.130 $mm^{-1}$ |
| F(000) | 752 |
| Crystal size | 0.38 x 0.35 x 0.12 $mm^3$ |
| Theta range for data collection | 2.44 to 25.04° |
| Index ranges | $-7 \le h \le 7$, $-10 \le k \le 10$, $-42 \le l \le 42$ |
| Reflections collected | 19057 |
| Independent reflections | 3465 [R(int) = 0.0282] |
| Completeness to theta = 25.04° | 99.2 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7452 and 0.6705 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3465 / 0 / 222 |
| Goodness-of-fit on $F^2$ | 1.081 |
| Final R indices [I>2sigma(I)] | R1 = 0.0303, wR2 = 0.0768 |
| R indices (all data) | R1 = 0.0312, wR2 = 0.0777 |
| Absolute structure parameter | 0.01(10) |
| Largest diff. peak and hole | 0.252 and -0.168 $e.Å^{-3}$ |

**Table A4.2:** Refined Positional Parameters for Compound (–)-**2.20**

| Atom | x | y | z | $U_{eq}$, $A^2$ |
|---|---|---|---|---|
| C1 | 0.2995(3) | 0.7318(2) | 0.07155(5) | 0.0326(4) |
| C2 | 0.2245(3) | 0.57633(19) | 0.05617(4) | 0.0286(4) |
| C3 | 0.3702(2) | 0.43837(18) | 0.06560(4) | 0.0221(3) |
| C4 | 0.3750(2) | 0.40996(18) | 0.10886(4) | 0.0211(3) |
| C5 | 0.7274(3) | 0.6284(2) | 0.14124(6) | 0.0444(5) |
| C6 | 0.3157(3) | 0.6088(2) | 0.18143(5) | 0.0372(4) |
| C7 | 0.1876(3) | 0.5963(2) | 0.01442(5) | 0.0428(4) |
| C8 | 0.2982(2) | 0.28668(18) | 0.04834(4) | 0.0239(3) |
| C9 | 0.4130(3) | 0.16307(19) | 0.05641(4) | 0.0255(3) |
| C10 | 0.5984(3) | 0.19199(18) | 0.08171(4) | 0.0260(3) |
| C11 | 0.5085(2) | 0.26232(18) | 0.11857(4) | 0.0240(3) |
| C12 | 0.6001(2) | 0.46234(19) | 0.05214(4) | 0.0286(4) |
| C13 | 0.7333(3) | 0.3201(2) | 0.06336(5) | 0.0300(4) |
| C14 | 0.7336(3) | 0.0478(2) | 0.08865(5) | 0.0350(4) |
| C15 | 0.3833(3) | 0.14229(18) | 0.14111(4) | 0.0295(4) |
| C16 | 0.3132(3) | 0.2040(2) | 0.17892(4) | 0.0323(4) |
| C17 | 0.2167(3) | 0.08159(18) | 0.20319(4) | 0.0281(3) |
| C18 | 0.0151(3) | 0.0007(2) | 0.19285(5) | 0.0342(4) |
| C19 | -0.0363(3) | -0.0997(2) | 0.22704(5) | 0.0385(4) |
| C20 | 0.1516(3) | -0.0815(2) | 0.25247(5) | 0.0383(4) |
| C21 | 0.2910(3) | 0.0325(2) | 0.23559(5) | 0.0353(4) |
| O1 | 0.3298(2) | 0.73512(13) | 0.11042(3) | 0.0381(3) |
| O2 | 0.1764(3) | -0.14927(19) | 0.28200(4) | 0.0620(5) |
| Si1 | 0.44008(7) | 0.59445(5) | 0.134833(12) | 0.02619(12) |

$U_{eq}={}^{1}/_{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

**Table A4.3:** Positional Parameters for Hydrogens in Compound (–)-**2.20**

| Atom | x | y | z | $U_{iso}$, $A^2$ |
|---|---|---|---|---|
| H1a | 0.4314 | 0.7588 | 0.0595 | 0.043 |
| H1b | 0.1972 | 0.8111 | 0.0650 | 0.043 |
| H2 | 0.0873 | 0.5545 | 0.0675 | 0.038 |
| H4 | 0.2299 | 0.3842 | 0.1158 | 0.028 |
| H5a | 0.7945 | 0.6351 | 0.1174 | 0.067 |
| H5b | 0.7873 | 0.5437 | 0.1551 | 0.067 |
| H5c | 0.7486 | 0.7240 | 0.1546 | 0.067 |
| H6a | 0.3397 | 0.7108 | 0.1915 | 0.056 |
| H6b | 0.3761 | 0.5321 | 0.1977 | 0.056 |
| H6c | 0.1669 | 0.5910 | 0.1792 | 0.056 |
| H7a | 0.0968 | 0.6840 | 0.0103 | 0.064 |
| H7b | 0.1228 | 0.5040 | 0.0046 | 0.064 |
| H7c | 0.3199 | 0.6135 | 0.0022 | 0.064 |
| H8 | 0.1804 | 0.2809 | 0.0330 | 0.032 |
| H9 | 0.3817 | 0.0647 | 0.0471 | 0.034 |
| H11 | 0.6281 | 0.2960 | 0.1338 | 0.032 |
| H12a | 0.6024 | 0.4748 | 0.0253 | 0.038 |
| H12b | 0.6583 | 0.5558 | 0.0633 | 0.038 |
| H13a | 0.8423 | 0.3528 | 0.0806 | 0.040 |
| H13b | 0.8017 | 0.2779 | 0.0414 | 0.040 |
| H14a | 0.6464 | -0.0351 | 0.0979 | 0.053 |
| H14b | 0.8404 | 0.0717 | 0.1067 | 0.053 |
| H14c | 0.7989 | 0.0160 | 0.0658 | 0.053 |
| H15a | 0.2600 | 0.1113 | 0.1270 | 0.039 |
| H15b | 0.4698 | 0.0504 | 0.1448 | 0.039 |
| H16a | 0.4340 | 0.2483 | 0.1916 | 0.043 |
| H16b | 0.2115 | 0.2869 | 0.1751 | 0.043 |
| H18a | 0.0342 | -0.0636 | 0.1709 | 0.045 |
| H18b | -0.0962 | 0.0755 | 0.1881 | 0.045 |
| H19a | -0.1638 | -0.0633 | 0.2391 | 0.051 |
| H19b | -0.0551 | -0.2078 | 0.2200 | 0.051 |
| H21 | 0.4164 | 0.0667 | 0.2462 | 0.047 |

**Table A4.4:** Refined Thermal Parameters (U's) for Compound (–)-**2.20**

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| C1 | 0.0371(9) | 0.0259(8) | 0.0347(9) | 0.0046(7) | -0.0068(7) | -0.0013(8) |
| C2 | 0.0257(8) | 0.0290(8) | 0.0311(8) | 0.0037(7) | -0.0054(6) | -0.0045(7) |
| C3 | 0.0219(7) | 0.0237(8) | 0.0208(7) | 0.0000(6) | -0.0005(6) | -0.0066(6) |
| C4 | 0.0195(7) | 0.0215(7) | 0.0224(7) | 0.0001(6) | 0.0006(5) | -0.0030(6) |
| C5 | 0.0364(10) | 0.0434(11) | 0.0535(12) | -0.0112(9) | -0.0093(9) | -0.0102(8) |
| C6 | 0.0505(11) | 0.0327(9) | 0.0283(8) | -0.0098(7) | -0.0006(8) | -0.0006(9) |
| C7 | 0.0519(11) | 0.0385(10) | 0.0379(10) | 0.0074(8) | -0.0171(8) | -0.0030(10) |
| C8 | 0.0193(7) | 0.0300(8) | 0.0222(7) | -0.0027(6) | 0.0018(6) | -0.0054(6) |
| C9 | 0.0242(8) | 0.0266(7) | 0.0258(7) | -0.0065(6) | 0.0054(6) | -0.0046(7) |
| C10 | 0.0224(8) | 0.0275(8) | 0.0281(8) | -0.0009(6) | 0.0019(6) | -0.0003(7) |
| C11 | 0.0248(7) | 0.0239(8) | 0.0233(7) | -0.0008(6) | -0.0024(6) | -0.0015(6) |
| C12 | 0.0248(8) | 0.0333(8) | 0.0276(8) | 0.0034(7) | 0.0034(6) | -0.0099(7) |
| C13 | 0.0185(8) | 0.0399(9) | 0.0317(8) | -0.0031(7) | 0.0024(7) | -0.0052(7) |
| C14 | 0.0316(9) | 0.0362(10) | 0.0374(9) | -0.0035(7) | 0.0009(7) | 0.0050(8) |
| C15 | 0.0358(9) | 0.0227(7) | 0.0301(8) | 0.0021(6) | 0.0009(7) | -0.0017(6) |
| C16 | 0.0425(10) | 0.0259(8) | 0.0284(8) | -0.0001(7) | 0.0014(8) | -0.0056(8) |
| C17 | 0.0361(9) | 0.0230(7) | 0.0252(7) | -0.0029(7) | 0.0047(7) | 0.0009(7) |
| C18 | 0.0396(10) | 0.0324(9) | 0.0305(9) | 0.0027(7) | -0.0023(8) | -0.0032(7) |
| C19 | 0.0422(10) | 0.0391(9) | 0.0342(9) | -0.0002(8) | 0.0105(8) | -0.0072(9) |
| C20 | 0.0530(11) | 0.0357(9) | 0.0262(8) | 0.0022(8) | 0.0059(8) | 0.0028(9) |
| C21 | 0.0378(10) | 0.0385(10) | 0.0296(8) | 0.0009(7) | -0.0016(8) | -0.0016(8) |
| O1 | 0.0568(8) | 0.0231(6) | 0.0342(6) | -0.0022(5) | -0.0084(6) | 0.0017(6) |
| O2 | 0.0825(11) | 0.0654(10) | 0.0381(8) | 0.0229(7) | -0.0041(8) | -0.0076(9) |
| Si1 | 0.0293(2) | 0.0228(2) | 0.0264(2) | -0.00349(18) | -0.00369(18) | -0.00263(19) |

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

**Table A4.5:** Bond Distances in Compound **(–)-2.20**, Å

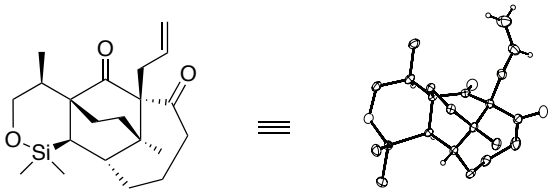
| | | | | | |
|---|---|---|---|---|---|
| C1-O1 | 1.411(2) | C1-C2 | 1.522(2) | C2-C7 | 1.529(2) |
| C2-C3 | 1.541(2) | C3-C8 | 1.514(2) | C3-C12 | 1.551(2) |
| C3-C4 | 1.575(2) | C4-C11 | 1.564(2) | C4-Si1 | 1.8848(15) |
| C5-Si1 | 1.8617(19) | C6-Si1 | 1.8569(17) | C8-C9 | 1.320(2) |
| C9-C10 | 1.508(2) | C10-C14 | 1.527(2) | C10-C13 | 1.543(2) |
| C10-C11 | 1.565(2) | C11-C15 | 1.533(2) | C12-C13 | 1.539(2) |
| C15-C16 | 1.526(2) | C16-C17 | 1.498(2) | C17-C21 | 1.326(2) |
| C17-C18 | 1.503(2) | C18-C19 | 1.537(2) | C19-C20 | 1.511(3) |
| C20-O2 | 1.221(2) | C20-C21 | 1.453(3) | O1-Si1 | 1.6494(13) |

**Table A4.6:** Bond Angles in Compound (–)-**2.20**, °

| | | | | | |
|---|---|---|---|---|---|
| O1-C1-C2 | 114.85(13) | C1-C2-C7 | 107.85(14) | C1-C2-C3 | 113.99(13) |
| C7-C2-C3 | 113.23(14) | C8-C3-C2 | 112.95(12) | C8-C3-C12 | 105.69(12) |
| C2-C3-C12 | 113.20(13) | C8-C3-C4 | 106.12(12) | C2-C3-C4 | 110.39(12) |
| C12-C3-C4 | 108.08(12) | C11-C4-C3 | 110.88(12) | C11-C4-Si1 | 116.87(10) |
| C3-C4-Si1 | 111.32(10) | C9-C8-C3 | 115.79(13) | C8-C9-C10 | 115.54(14) |
| C9-C10-C14 | 113.80(14) | C9-C10-C13 | 107.02(13) | C14-C10-C13 | 109.66(13) |
| C9-C10-C11 | 106.86(12) | C14-C10-C11 | 112.30(13) | C13-C10-C11 | 106.84(12) |
| C15-C11-C10 | 112.18(12) | C15-C11-C4 | 112.46(12) | C10-C11-C4 | 108.75(12) |
| C13-C12-C3 | 109.26(12) | C12-C13-C10 | 111.90(13) | C16-C15-C11 | 112.89(13) |
| C17-C16-C15 | 113.27(13) | C21-C17-C16 | 126.15(16) | C21-C17-C18 | 111.94(15) |
| C16-C17-C18 | 121.90(14) | C17-C18-C19 | 104.01(14) | C20-C19-C18 | 105.00(15) |
| O2-C20-C21 | 127.32(19) | O2-C20-C19 | 125.37(19) | C21-C20-C19 | 107.30(14) |
| C17-C21-C20 | 111.40(16) | C1-O1-Si1 | 124.78(11) | O1-Si1-C6 | 104.55(8) |
| O1-Si1-C5 | 111.53(9) | C6-Si1-C5 | 107.13(9) | O1-Si1-C4 | 105.00(6) |
| C6-Si1-C4 | 114.20(7) | C5-Si1-C4 | 114.07(8) | | |

# Appendix 5: X-Ray Crystallographic Data for Compound (+)-3.4

## X-ray Structure Determination of Compound (+)-3.4



Compound (+)-**3.4**, $C_{21}H_{32}SiO_3$, crystallizes in the orthorhombic space group $P2_12_12_1$ (systematic absences h00: h=odd, 0k0: k=odd, and 00l: l=odd) with a=9.5916(4)Å, b=11.3171(5)Å, c=18.2254(8)Å, V=1978.35(15)Å$^3$, Z=4, and $d_{calc}$=1.211 g/cm$^3$ . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-K$\alpha$ radiation ($\lambda$=0.71073 Å) at a temperature of 143(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 5 seconds. A total of 1729 frames were collected with a crystal to detector distance of 37.596 mm, rotation widths of 0.5° and exposures of 5 seconds:

| scan type | 2θ | ω | ϕ | χ | frames |
|---|---|---|---|---|---|
| ϕ | -15.50 | 258.48 | -311.30 | 19.46 | 658 |
| ϕ | -15.50 | -10.67 | -119.39 | -77.44 | 173 |
| ω | 4.50 | -102.77 | -128.06 | 52.47 | 159 |
| ϕ | 19.50 | -32.21 | -344.03 | 36.30 | 739 |

Rotation frames were integrated using SAINT, producing a listing of unaveraged $F^2$ and $\sigma(F^2)$ values which were then passed to the SHELXTL program package for further processing and structure solution. A total of 30835 reflections were measured over the ranges $2.12 \leq \theta \leq 25.14°$, $-11 \leq h \leq 11$, $-13 \leq k \leq 13$, $-21 \leq l \leq 21$ yielding 3543 unique reflections (Rint = 0.0314). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS (minimum and maximum transmission 0.6911, 0.7452).

The structure was solved by direct methods (SHELXS-97). Refinement was by full-matrix least squares based on $F^2$ using SHELXL-97. All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ (0.0435P)^2 + 0.3812P]$ where $P = (F_o^2 + 2F_c^2)/3$.

Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.0278 and wR2=0.0756 for 3429 observed reflections for which $F > 4\sigma(F)$ and R1=0.0288 and wR2=0.0762 and GOF =1.051 for all 3543 unique, non-zero reflections and 231 variables. The maximum $\Delta/\sigma$ in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were +0.218 and -0.133 e/Å$^3$.

Table A4.1 lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables A4.2 and A4.3. Anisotropic thermal parameters are in Table A5.4. Tables A5.5 and A5.6 list bond distances and bond angles. Figure A5.1 is an ORTEP representation of the molecule with 30% probability thermal ellipsoids displayed.

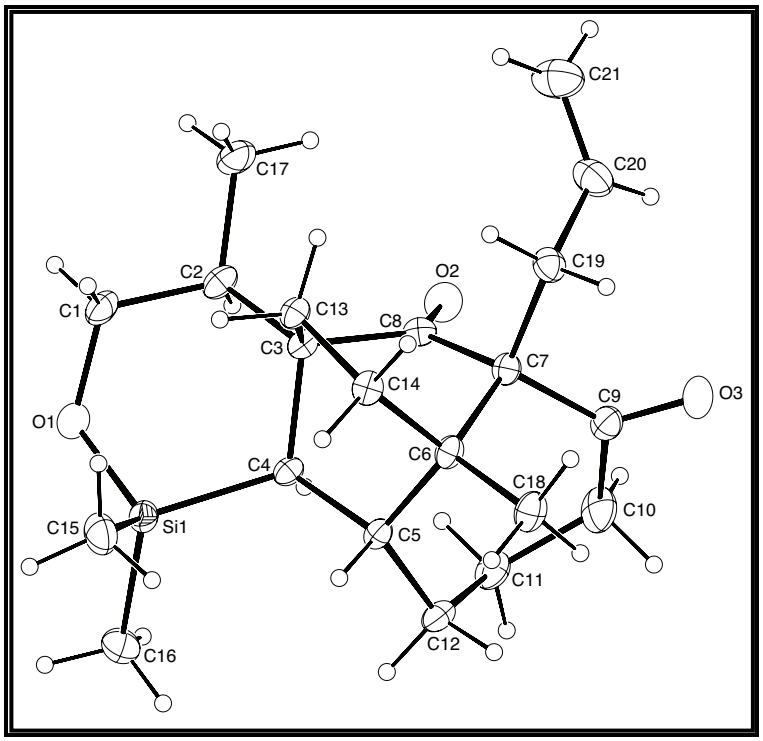



**Figure A5.1:** ORTEP drawing of Compound (+)-**3.4** with 30% probability thermal ellipsoids.

**Table A5.1:** Summary of Structure Determination of Compound (+)-**3.4**

| | |
|---|---|
| Empirical formula | $C_{21}H_{32}SiO_3$ |
| Formula weight | 360.56 |
| Temperature | 143(1) K |
| Wavelength | 0.71073 Å |
| Crystal system | orthorhombic |
| Space group | $P2_12_12_1$ |
| Cell constants: | |
| a | 9.5916(4) Å |
| b | 11.3171(5) Å |
| c | 18.2254(8) Å |
| Volume | 1978.35(15) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.211 $Mg/m^3$ |
| Absorption coefficient | 0.135 $mm^{-1}$ |
| F(000) | 784 |
| Crystal size | 0.42 x 0.28 x 0.18 $mm^3$ |
| Theta range for data collection | 2.12 to 25.14° |
| Index ranges | $-11 \leq h \leq 11$, $-13 \leq k \leq 13$, $-21 \leq l \leq 21$ |
| Reflections collected | 30835 |
| Independent reflections | 3543 [R(int) = 0.0314] |
| Completeness to theta = 25.14° | 99.8 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7452 and 0.6911 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3543 / 0 / 231 |
| Goodness-of-fit on $F^2$ | 1.051 |
| Final R indices [I>2sigma(I)] | R1 = 0.0278, wR2 = 0.0756 |
| R indices (all data) | R1 = 0.0288, wR2 = 0.0762 |
| Absolute structure parameter | 0.11(10) |
| Largest diff. peak and hole | 0.218 and -0.133 $e.Å^{-3}$ |

**Table A5.2:** Refined Positional Parameters for Compound (+)-**3.4**

| Atom | x | y | z | $U_{eq}$, $A^2$ |
|---|---|---|---|---|
| C1 | 0.52044(17) | 0.51978(15) | 0.34842(8) | 0.0321(4) |
| C2 | 0.44319(16) | 0.47741(13) | 0.28039(8) | 0.0278(3) |
| C3 | 0.51306(14) | 0.51550(11) | 0.20786(7) | 0.0212(3) |
| C4 | 0.66587(14) | 0.46686(12) | 0.20245(8) | 0.0214(3) |
| C5 | 0.73211(14) | 0.49650(13) | 0.12653(7) | 0.0225(3) |
| C6 | 0.63209(16) | 0.57570(12) | 0.08098(8) | 0.0235(3) |
| C7 | 0.48988(14) | 0.50994(13) | 0.06767(7) | 0.0235(3) |
| C8 | 0.44794(15) | 0.45484(12) | 0.14121(8) | 0.0235(3) |
| C9 | 0.50556(16) | 0.41801(14) | 0.00527(8) | 0.0295(3) |
| C10 | 0.5845(2) | 0.30378(15) | 0.01287(10) | 0.0433(4) |
| C11 | 0.68466(19) | 0.28435(14) | 0.07633(9) | 0.0337(4) |
| C12 | 0.78824(17) | 0.38415(13) | 0.08891(8) | 0.0297(3) |
| C13 | 0.51603(15) | 0.65061(12) | 0.19759(8) | 0.0237(3) |
| C14 | 0.60392(16) | 0.68472(12) | 0.13007(8) | 0.0244(3) |
| C15 | 0.85136(19) | 0.64960(15) | 0.28861(10) | 0.0397(4) |
| C16 | 0.91047(18) | 0.38613(16) | 0.29630(10) | 0.0398(4) |
| C17 | 0.29055(16) | 0.51761(16) | 0.28545(9) | 0.0378(4) |
| C18 | 0.70002(18) | 0.61694(14) | 0.00951(8) | 0.0324(4) |
| C19 | 0.37065(16) | 0.59626(14) | 0.04413(9) | 0.0303(3) |
| C20 | 0.22989(18) | 0.54066(16) | 0.03892(10) | 0.0413(4) |
| C21 | 0.1215(2) | 0.5740(2) | 0.07503(13) | 0.0565(5) |
| O1 | 0.66066(12) | 0.47773(11) | 0.35393(6) | 0.0388(3) |
| O2 | 0.37674(12) | 0.36660(9) | 0.14433(6) | 0.0340(3) |
| O3 | 0.45467(14) | 0.43917(12) | -0.05448(6) | 0.0430(3) |
| Si1 | 0.77234(4) | 0.49960(4) | 0.28640(2) | 0.02731(11) |

$U_{eq}={}^{1}/_{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

**Table A5.3:** Positional Parameters for Hydrogens in Compound (+)-**3.4**

| Atom | x | y | z | $U_{iso}$, $A^2$ |
|---|---|---|---|---|
| H1a | 0.5217 | 0.6055 | 0.3484 | 0.043 |
| H1b | 0.4693 | 0.4944 | 0.3915 | 0.043 |
| H2 | 0.4434 | 0.3908 | 0.2815 | 0.037 |
| H4 | 0.6554 | 0.3807 | 0.2023 | 0.028 |
| H5 | 0.8140 | 0.5454 | 0.1371 | 0.030 |
| H10a | 0.6373 | 0.2929 | -0.0320 | 0.058 |
| H10b | 0.5161 | 0.2408 | 0.0148 | 0.058 |
| H11a | 0.7363 | 0.2120 | 0.0675 | 0.045 |
| H11b | 0.6307 | 0.2733 | 0.1208 | 0.045 |
| H12a | 0.8268 | 0.4067 | 0.0417 | 0.040 |
| H12b | 0.8644 | 0.3536 | 0.1184 | 0.040 |
| H13a | 0.5551 | 0.6873 | 0.2411 | 0.031 |
| H13b | 0.4216 | 0.6797 | 0.1914 | 0.031 |
| H14a | 0.6919 | 0.7181 | 0.1461 | 0.032 |
| H14b | 0.5550 | 0.7444 | 0.1019 | 0.032 |
| H15a | 0.7791 | 0.7077 | 0.2936 | 0.060 |
| H15b | 0.9017 | 0.6632 | 0.2439 | 0.060 |
| H15c | 0.9141 | 0.6553 | 0.3295 | 0.060 |
| H16a | 0.9582 | 0.3974 | 0.3421 | 0.060 |
| H16b | 0.9757 | 0.3934 | 0.2566 | 0.060 |
| H16c | 0.8691 | 0.3089 | 0.2954 | 0.060 |
| H17a | 0.2492 | 0.4861 | 0.3292 | 0.057 |
| H17b | 0.2402 | 0.4896 | 0.2434 | 0.057 |
| H17c | 0.2868 | 0.6023 | 0.2869 | 0.057 |
| H18a | 0.7851 | 0.6580 | 0.0204 | 0.049 |
| H18b | 0.6376 | 0.6690 | -0.0160 | 0.049 |
| H18c | 0.7201 | 0.5497 | -0.0208 | 0.049 |
| H19a | 0.3663 | 0.6606 | 0.0792 | 0.040 |
| H19b | 0.3942 | 0.6299 | -0.0032 | 0.040 |
| H20 | 0.2197 | 0.4770 | 0.0071 | 0.055 |
| H21a | 0.1276 | 0.6373 | 0.1074 | 0.075 |
| H21b | 0.0372 | 0.5347 | 0.0688 | 0.075 |

**Table A5.4:** Refined Thermal Parameters (U's) for Compound (+)-**3.4**

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| C1 | 0.0382(8) | 0.0362(9) | 0.0217(7) | 0.0025(6) | 0.0087(6) | 0.0059(7) |
| C2 | 0.0340(8) | 0.0229(7) | 0.0265(7) | 0.0009(6) | 0.0102(6) | -0.0007(6) |
| C3 | 0.0239(6) | 0.0174(6) | 0.0222(7) | 0.0008(6) | 0.0041(5) | -0.0005(5) |
| C4 | 0.0252(7) | 0.0167(6) | 0.0223(7) | -0.0003(5) | 0.0040(6) | 0.0022(5) |
| C5 | 0.0245(6) | 0.0224(6) | 0.0207(7) | -0.0023(6) | 0.0039(5) | -0.0029(6) |
| C6 | 0.0294(7) | 0.0211(7) | 0.0201(7) | 0.0004(6) | 0.0032(6) | -0.0033(6) |
| C7 | 0.0272(7) | 0.0208(7) | 0.0225(7) | -0.0008(6) | -0.0002(5) | -0.0013(6) |
| C8 | 0.0224(7) | 0.0193(6) | 0.0287(8) | 0.0004(6) | 0.0026(6) | 0.0001(6) |
| C9 | 0.0281(8) | 0.0312(8) | 0.0291(8) | -0.0056(7) | 0.0019(6) | -0.0070(6) |
| C10 | 0.0588(12) | 0.0317(9) | 0.0395(9) | -0.0137(7) | -0.0061(8) | 0.0014(8) |
| C11 | 0.0456(9) | 0.0227(7) | 0.0327(8) | -0.0080(6) | 0.0035(7) | 0.0053(7) |
| C12 | 0.0317(8) | 0.0308(8) | 0.0268(7) | -0.0037(6) | 0.0076(7) | 0.0051(7) |
| C13 | 0.0292(7) | 0.0184(7) | 0.0233(7) | -0.0014(5) | 0.0023(6) | 0.0016(6) |
| C14 | 0.0310(8) | 0.0173(6) | 0.0249(7) | 0.0015(6) | 0.0010(6) | -0.0034(6) |
| C15 | 0.0440(10) | 0.0392(9) | 0.0360(9) | -0.0077(8) | -0.0101(8) | -0.0002(8) |
| C16 | 0.0371(9) | 0.0417(9) | 0.0406(9) | 0.0005(8) | -0.0058(8) | 0.0126(7) |
| C17 | 0.0313(8) | 0.0458(10) | 0.0363(9) | -0.0043(8) | 0.0116(7) | -0.0040(7) |
| C18 | 0.0421(9) | 0.0311(8) | 0.0241(7) | 0.0039(6) | 0.0054(7) | -0.0079(7) |
| C19 | 0.0327(8) | 0.0287(7) | 0.0295(8) | 0.0009(7) | -0.0041(7) | 0.0030(7) |
| C20 | 0.0345(8) | 0.0366(9) | 0.0527(11) | -0.0084(8) | -0.0116(8) | 0.0026(7) |
| C21 | 0.0378(10) | 0.0553(12) | 0.0763(15) | -0.0072(11) | 0.0053(10) | -0.0020(9) |
| O1 | 0.0406(6) | 0.0545(8) | 0.0213(5) | 0.0070(5) | 0.0022(5) | 0.0138(6) |
| O2 | 0.0373(6) | 0.0269(5) | 0.0378(6) | -0.0004(5) | 0.0040(5) | -0.0121(5) |
| O3 | 0.0476(7) | 0.0547(8) | 0.0266(6) | -0.0075(5) | -0.0052(6) | 0.0021(6) |
| Si1 | 0.0307(2) | 0.0299(2) | 0.0213(2) | -0.00067(17) | -0.00138(15) | 0.00650(18) |

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

**Table A5.5:** Bond Distances in Compound (+)-**3.4**, Å

| | | | | | |
|---|---|---|---|---|---|
| C1-O1 | 1.430(2) | C1-C2 | 1.522(2) | C2-C17 | 1.536(2) |
| C2-C3 | 1.5436(18) | C3-C8 | 1.5288(19) | C3-C13 | 1.5407(19) |
| C3-C4 | 1.5687(18) | C4-C5 | 1.5591(18) | C4-Si1 | 1.8765(15) |
| C5-C12 | 1.5417(19) | C5-C6 | 1.553(2) | C6-C18 | 1.529(2) |
| C6-C14 | 1.5479(19) | C6-C7 | 1.573(2) | C7-C8 | 1.5319(19) |
| C7-C9 | 1.549(2) | C7-C19 | 1.564(2) | C8-O2 | 1.2110(18) |
| C9-O3 | 1.217(2) | C9-C10 | 1.505(2) | C10-C11 | 1.519(2) |
| C11-C12 | 1.522(2) | C13-C14 | 1.5409(19) | C15-Si1 | 1.8595(18) |
| C16-Si1 | 1.8538(16) | C19-C20 | 1.493(2) | C20-C21 | 1.287(3) |
| O1-Si1 | 1.6502(12) | | | | |

**Table A5.6:** Bond Angles in Compound (+)-**3.4**, °

| | | | | | |
|---|---|---|---|---|---|
| O1-C1-C2 | 114.22(12) | C1-C2-C17 | 108.78(12) | C1-C2-C3 | 113.47(12) |
| C17-C2-C3 | 112.49(12) | C8-C3-C13 | 110.90(11) | C8-C3-C2 | 112.19(11) |
| C13-C3-C2 | 112.90(11) | C8-C3-C4 | 100.04(10) | C13-C3-C4 | 108.86(11) |
| C2-C3-C4 | 111.19(11) | C5-C4-C3 | 111.16(11) | C5-C4-Si1 | 117.35(9) |
| C3-C4-Si1 | 112.83(9) | C12-C5-C6 | 116.99(12) | C12-C5-C4 | 111.08(12) |
| C6-C5-C4 | 110.29(11) | C18-C6-C14 | 108.87(12) | C18-C6-C5 | 111.60(13) |
| C14-C6-C5 | 105.00(11) | C18-C6-C7 | 112.50(12) | C14-C6-C7 | 108.36(12) |
| C5-C6-C7 | 110.18(11) | C8-C7-C9 | 113.24(12) | C8-C7-C19 | 107.59(12) |
| C9-C7-C19 | 106.81(12) | C8-C7-C6 | 106.59(11) | C9-C7-C6 | 110.30(11) |
| C19-C7-C6 | 112.39(12) | O2-C8-C3 | 124.29(13) | O2-C8-C7 | 121.66(13) |
| C3-C8-C7 | 113.89(11) | O3-C9-C10 | 116.96(14) | O3-C9-C7 | 119.07(14) |
| C10-C9-C7 | 123.94(13) | C9-C10-C11 | 120.84(13) | C10-C11-C12 | 114.83(14) |
| C11-C12-C5 | 116.82(13) | C3-C13-C14 | 110.84(11) | C13-C14-C6 | 110.95(11) |
| C20-C19-C7 | 114.55(13) | C21-C20-C19 | 125.07(17) | C1-O1-Si1 | 120.54(9) |
| O1-Si1-C16 | 106.70(7) | O1-Si1-C15 | 112.67(8) | C16-Si1-C15 | 109.81(9) |
| O1-Si1-C4 | 103.02(6) | C16-Si1-C4 | 109.36(7) | C15-Si1-C4 | 114.82(7) |

## About the Author

Artem Shvartsbart was born in St. Petersburg, Russia to Michael Shvartsbart and Yelena Ilina in 1986. He immigrated to the USA in 1989, and grew up in Glen Cove on Long Island. He attended Portledge high school where, during his junior year, he discovered his interest in chemistry. In January of 2005, Artem moved on to Brandeis University, where he became fascinated and intrigued by organic chemistry after taking the introductory course. He found that he particularly enjoyed solving synthetic problems. Artem then took every graduate organic chemistry course offered at Brandeis. In the summer of 2007, he was fortunate enough to be admitted into the laboratory of Professor Barry Snider for the summer of 2007 and for the duration of his senior year, where he worked on the total synthesis of (–)-berkelic acid. It was during this time that Artem realized his passion for laboratory research and natural products synthesis. Pursuing a Ph.D. in organic chemistry required no deliberation at all. After graduating from Brandeis cum laude with a B.S. in chemistry with highest honors, he spent the following summer in a medicinal chemistry internship at the Novartis Institute in Cambridge, MA. In the summer of 2008, Artem entered the University of Pennsylvania as a graduate student. He then joined the research group of Professor Amos Smith, where he designed and implemented a successful total synthesis of the complex *Daphniphyllum* alkaloid (–)-calyciphylline N. Following graduation, Artem will begin his post-doctoral training at the Memorial Sloan-Kettering Institute under the supervision of Professor Samuel Danishefsky.